Chapter 9

The Role of Chemotherapy in Recurrent Ovarian Cancer

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1. Introduction

Epithelial ovarian cancer causes more deaths than any other cancer of the female reproductive system and it is the leading cause of death from gynecologic cancer. There is no universally accepted consensus on the surveillance of ovarian cancer, but if we review the main clinical guidelines, we can find similar recommendations for follow-up for patients with ovarian cancer after chemotherapy treatment.

Approximately 60% of patients will experience a relapse after the standard first-line treatment including cytoreductive surgery and adjuvant chemotherapy [1]. At this time, when relapse occurs, the chance of cure decreases drastically and treatment is solely palliative. This makes the increase in overall survival and the quality of life the primary endpoints. Surgery is not sufficiently validated due to the lack of phase III clinical trials, and there are no approved targeted therapies in relapsed ovarian cancer. Therefore, chemotherapy is the only option to achieve these objectives. We will review the role of chemotherapy in recurrent ovarian cancer in this chapter.

2. Diagnosis of epithelial ovarian cancer relapse

In stages I, II, III and IV complete responders, American guidelines recommend that, after completing primary surgery and adjuvant chemotherapy, follow-up visits should include a physical examination with a pelvic exam every 2 to 4 months for the first two years, then every 3 to 6 months until the fifth year, and then annually after the fifth year. Periodic monitoring of CA 125 and other tumor markers (e.g., CA 19.9, CEA) are also recommended if the markers were elevated previously. The rest of the examination, which ranges from performing

Computerized Tomography (CT), Magnetic Resonance Imaging (MRI) or Positron Emission Tomography/Computerized Tomography (PET/CT), will be performed as clinically indicated such as weight loss, fatigue, bloating, pelvic pain or bowel occlusion [2].

European clinical guidelines recommend a physical exam and routine measurement of CA 125 every 3 months for 2 years, every 4 months during the third year and every 6 months during years 4 and 5. CT scan will be performed if the CA 125 is elevated or if there is clinical evidence of relapse [3].

A physical examination to detect recurrent ovarian cancer has limited value and detects abnormalities that indicate a recurrence only in 3.8 to 4.6% of patients [4, 5]. CT has a sensitivity of 40 - 93%, depending on the presence of peritoneal disease, tumor location and the presence of ascites. The sensitivity of MRI ranges from 62 to 91%, depending on the location of the tumor and tumor size. MRI facilitates the detection of disease on the peritoneal and intestinal surface [6].

We can define the relapse of ovarian cancer with the RECIST (Response Evaluation Criteria in Solid Tumors) criteria. However, relapse can also be defined as a doubling from the upper limit of normal value of CA 125 (30 U/mL) in patients who normalized their value after finishing their treatment, or doubling this value from the nadir (minimum value) in patients who never had normalized values [7-9]. It is estimated that this rise in the CA 125 level precedes the clinical detection of recurrence by about three months [10], and this may have implications at the beginning of the second-line treatment.

3. Classification of relapse

There are several classifications of patients with relapsed ovarian cancer based on the platinum-free interval (Table 1).

Markman suggested that the probability of response in the re-treatment with platinum-based chemotherapy depends on the platinum-free interval. In a retrospective analysis conducted at the Memorial Sloan-Kettering Cancer Center (New York, United States of America), these authors found a subgroup of patients with a higher likelihood of response to platinum salts. They selected 82 patients who received initial chemotherapeutic treatment with a cisplatin-based regimen and second-line treatment with a cisplatin- or carboplatin-based regimen, with a platinum-free interval of more than 4 months. The response rate to second-line treatment in the three groups according to the platinum-free interval at 5 to 12 months, 13 to 24 months and more than 24 months, was 27%, 33% and 59%, respectively [11]. They proposed to classify patients into different groups according to their previous response to platinum-based treatment and platinum-free interval: primary platinum-resistant (patients who progressed before the completion of the planned treatment), secondary platinum-resistant (patients who responded to a platinum regimen and did not respond to a second platinum-based treatment), and potentially platinum-sensitive (all patients who respond to a platinum-based treatment, subdivided into patients with platinum-free intervals of less than 6, 6 to 12 months and more than 12 months) [12].

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In 1993, Thigpen defined two subgroups of patients with relapsed ovarian carcinoma based on the volume of relapse and the time to relapse after the end of treatment with platinum. Patients with small-volume disease confined to the peritoneal cavity have a far better chance of achieving a response to second-line chemotherapy with subsequent prolonged survival than those with bulky disease or disease outside the abdomen. Thus, we can classify the patients into those who are still "clinically sensitive" to the platinum-based regimens (initial response to platinum-based therapy and relapse more than 6 months after cessation of treatment) and those with "clinically resistant" disease (defined as progression disease during or within 6 months of first-line treatment platinum-based therapy). We should choose a platinum-containing regimen for relapse for those patients classified as clinically sensitive and an alternative treatment without platinum salts for those with clinically resistant disease [13]. Until recently, this was the most utilized and simplest classification.

Author	Best response to platinum	Platinum Free Interval	Classification
Markman [11,12]	Progression	-----	Primary Platinum-resistant
	No response	Any	Primary Platinum-resistant
	Response	< 6 months	Potentially platinum-sensitive
	Response	> 6 months	Potentially platinum-sensitive
Thigpen [13]	Progression	----	Platinum-resistant
	No response	Any	Platinum-resistant
	Response	< 6 months	Platinum-resistant
	Response	> 6 months	Platinum-sensitive
1998 International Workshop Consensus [14]	Progression	----	Platinum-refractory
	No response	Any	Platinum-refractory
	Response	< 4 months	Platinum-refractory
	Response	> 4 - 12 months	Intermediate platinum-sensitive
	Response	> 12 months	Platinum-sensitive
NICE 2005 [15]	Progression	----	Platinum-refractory
	No response	Any	Platinum-refractory
2010 GCIG Consensus [16]	Response	< 6 months	Platinum-resistant
	Response	> 6 - 12 months	Partially platinum-sensitive
	Response	> 12 months	Platinum-sensitive

Table 1. Classification of relapsed ovarian cancer

The International Workshop Consensus established a different classification in 1998 and stratified patients into platinum-refractory (progression during or within 4 months), intermediate platinum-sensitive (initial response but relapse 4 -12 months) and platinum-sensitive (relapse after 12 months) [14].

More recently, the National Institute for Health and Clinical Excellence (NICE) in 2005 [15] and the Gynecologic Cancer InterGroup (GCIG) in 2010 [16] have developed new classifications, including partially platinum-sensitive patients (those who relapse between 6 and 12 months after completion of initial platinum-based chemotherapy).

4. Treatment of platinum-sensitive disease

Until the early 2000s, monotherapy with platinum salts was the standard treatment for patients with platinum-sensitive disease because clinical trials attempting to prove the superiority of polychemotherapy were negative.

More recent clinical trials have demonstrated the superiority of polychemotherapy versus monotherapy, making this strategy the standard treatment in patients with platinum-sensitive disease. We discuss the main previous studies in this section.

4.1. Carboplatin versus carboplatin/paclitaxel (ICON4/AGO-OVAR 2.2)

In parallel, two pragmatic clinical trials were designed to determine whether the combination of carboplatin and paclitaxel should be used at first relapse after platinum-based chemotherapy [the International Collaborative Ovarian Neoplasm 4 (ICON4), coordinated by the Instituto Mario Negri, Milan, Italy (IRFMN) and the Medical Research Council's Clinical Trials Unit, London, United Kingdom (MRC CTU), and Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) OVAR 2.2 coordinated by AGO, Karlsruhe, Germany] [17].

They randomized 802 patients with relapsed epithelial ovarian cancer who previously received platinum-based chemotherapy and had a platinum-free interval of more than 6 months (more than 12 months in the ICON4 group) to receive a conventional platinum-based chemotherapy (the majority of patients (71%) received carboplatin alone) or a combined treatment with paclitaxel 175 mg/m^2 plus cisplatin 50 mg/m^2 or carboplatin AUC 5 – 6 every 3 weeks for at least 6 cycles. The primary endpoint was overall survival (OS), and secondary endpoints were progression-free survival (PFS) and quality of life. The platinum-free interval was greater than 12 months in 75% of patients.

Patients in the AGO protocol must have previously received cisplatin or carboplatin plus paclitaxel, patients in the MRC CTU protocol trial were permitted to have had more than one line of previous chemotherapy and patients randomized into the Italian protocol required measurable disease.

With a median follow-up of 42 months, OS was increased by 5 months (24 versus 29 months), with an absolute difference in 2-year survival of 7% in favor of paclitaxel plus platinum-based

chemotherapy (57% versus 50%; Hazard Ratio (HR): 0.82; 95% CI 0.69 - 0.97; p = 0.02). For PFS, there was a HR: 0.76 (95% CI 0.66 - 0.89; p = 0.0004) in favor of paclitaxel plus platinum-based chemotherapy, which translates into an absolute difference in median PFS of 3 months in favor of the combination regimen (9 versus 12 months). The response rate (RR) seemed to be higher in the combination arm (66%) compared to the conventional chemotherapy arm (p = 0.06). There were no differences between the quality of life measures in both groups. The results showed no difference between different subgroups (randomization group, time to relapse, number of previous lines of chemotherapy, type of prior chemotherapy, age and performance status).

Paclitaxel plus platinum-based chemotherapy was generally more toxic than conventional platinum-based chemotherapy, causing more alopecia and neurotoxicity (20% of patients), while conventional platinum-based chemotherapy was associated with more hematological toxic effects than paclitaxel plus platinum chemotherapy.

The ICON4/AGO-OVAR 2.2 trial was the first large clinical trial that showed the superiority of polychemotherapy versus monotherapy in platinum-sensitive ovarian cancer.

Similar results were found in a Spanish randomized phase II clinical trial conducted by GEICO (Grupo Español de Investigación en Cáncer de Ovario) [18]. In this trial, 81 patients with platinum-sensitive recurrent ovarian carcinoma were randomized to carboplatin or carboplatin plus paclitaxel. The primary endpoint was objective response and secondary endpoints were time to progression, overall survival, tolerability and quality of life. The platinum-free interval was greater than 12 months in 57.7% of patients. In the intent-to-treat analysis, they reported a higher response rate in the group treated with carboplatin plus paclitaxel than in the carboplatin group (75.6% versus 50%; p = 0.017). The median time to progression (49.1 versus 33.7 weeks; p = 0.021) and overall survival (not reached versus 72.7 weeks; p = 0.0021) were also better in the group treated with the combination therapy. There were no differences in the quality of life. As in the ICON4/AGO-OVAR 2.2 trial, alopecia (86.8%) and neurotoxicity (23.7%) were more frequent in patients treated with paclitaxel. Stomatitis (18.4%) and myalgias/arthralgias (36.8%) were also more frequent in this group. In the ICON4/AGO OVAR 2.2 trial, only 40% of patients received paclitaxel as part of a previous treatment, which could affect the superiority of the paclitaxel arm following the relapse. In the Spanish trial, 87.2% of patients received paclitaxel previously, so it was suggested that carboplatin plus paclitaxel could be administered at relapse in patients who received this treatment as first-line therapy.

4.2. Carboplatin versus carboplatin/gemcitabine (AGO-OVAR 2.5)

Neurotoxicity is the main drawback for the re-treatment with carboplatin plus paclitaxel because, among other factors, co-administration of paclitaxel and platinum compounds can increase the development of neurotoxicity [19]. Neurotoxicity is a cumulative dose-dependent toxicity; 715 mg/m^2 is the mean cumulative dose to onset of grade 2 or greater neurotoxicity [20].

In the ICON4-AGO OVAR 2.2 study, moderate or severe neurological effects were observed in 20% of patients in the combination arm, and the majority of patients experienced grades 1

to 4 neurotoxicity (75% to 83%) with the combination of carboplatin–paclitaxel and cisplatin-paclitaxel.

For these reasons, an alternative combination with carboplatin and gemcitabine was designed to avoid toxic effects, such as neurotoxicity, derived from the combination of carboplatin or cisplatin and paclitaxel.

In the AGO-OVAR 2.5 [21] clinical trial, the AGO-OVAR investigators, in collaboration with the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and the European Organization for Research and Treatment of Cancer Gynecological Cancer Group (EORTC GCG), randomized 356 patients with platinum-sensitive recurrent ovarian cancer to receive either carboplatin alone (AUC 5) every 21 days or carboplatin AUC 4 on day 1 plus gemcitabine 1000 mg/m^2 on days 1 and 8, every 21 days. Patients could receive 6 to 10 cycles in both arms. The primary objective was progression-free survival, and secondary objectives included the response rate, duration of response, overall survival, quality of life and toxicity. Both groups were well balanced: 70.8% of patients had received platinum-based plus taxane as first-line therapy, and 59.8% of patients had a platinum-free interval greater than 12 months. The study was not powered to detect differences in OS.

With a median follow-up of 17 months, the median PFS in the combination arm and the single-agent arm were 8.6 months (95% CI, 7.9 - 9.7) and 5.8 months (95% CI, 5.2 - 7.1), respectively, with a 28% reduction in the progression-free event rate (HR: 0.72; 95% CI, 0.58 - 0.90; p = 0.0031). On the other hand, the RR was significantly higher in the gemcitabine plus carboplatin arm than in the carboplatin arm (47.2% versus 30.9%; p = 0.0016). The HR for overall survival was 0.96 (95% CI, 0.75 - 1.23; p = 0.7349). There was no difference in OS, which was 18 months for patients treated with carboplatin and gemcitabine versus 17.3 for patients treated with carboplatin alone. Furthermore, there was no difference in the quality of life between treatment arms.

A significant increase in serious (grade 3 to 4) hematologic adverse events was documented in both arms, including neutropenia (71% versus 12%), thrombocytopenia (35% versus 11%) and anemia (27% versus 8%). These adverse events appeared more commonly in the combination arm. The use of granulocyte colony-stimulating factor was more frequent in patients treated with carboplatin and gemcitabine (24% versus 10%).

The results of the AGO-OVAR 2.5 trial confirmed the superiority of platinum-based polychemotherapy over platinum salts in monotherapy.

The results of this clinical trial provide a treatment alternative to carboplatin/paclitaxel, with a different profile of toxicity, including less alopecia and neurotoxicity, which can affect the quality of life for women with ovarian cancer.

4.3. Carboplatin/paclitaxel versus carboplatin/Pegylated Liposomal Doxorubicin (PLD) (CALYPSO)

In an attempt to establish a new second-line treatment with improved tolerance and equal or greater efficacy than the standard treatment with carboplatin and paclitaxel, the CALYPSO clinical trial was designed [22].

In this trial, a total of 976 patients with histologically confirmed ovarian cancer with recurrence more than 6 months after first- or second-line platinum- and taxane-based therapies were randomly assigned to receive carboplatin AUC 5 on day 1 plus pegylated liposomal doxorubicin (PLD) 30 mg/m^2 on day 1, every 28 days, or carboplatin AUC 5 on day 1 plus paclitaxel 175 mg/m2 on day 1 at 3-week intervals for at least 6 cycles (in case of stabilization of disease or if partial response was achieved after 6 courses, the patients were allowed to receive therapy until progression). The platinum-free interval was greater than 12 months in 63.9% of patients.

The study was designed as a non-inferiority trial. The primary endpoint was progression-free survival, and secondary endpoints were toxicity, quality of life, and overall survival.

With a median follow-up of 22 months, PFS was statistically superior for patients treated with carboplatin/PLD than patients in the carboplatin/paclitaxel arm (11.3 versus 9.4 months with HR: 0.821; 95% CI, 0.72 to 0.94; p = 0.005).

Severe non-hematologic toxicity (grades 3 to 4) was more frequent in patients in the carboplatin/paclitaxel arm than in patients treated with carboplatin/PLD (36.8% versus 28.4%; p = 0.001). Grade 2 or greater palmar-plantar erythrodisestesia (12% versus 2.2%), nausea (35.2% versus 24.2%), vomiting (22.5% versus 15.6%) and mucositis (13.9% versus 7%) occurred more commonly in the carboplatin/PLD arm. Grade 2 or greater neurotoxicity (4.9% versus 26.9%), complete hair loss (7% versus 83.6%) and allergic/hypersensitivity reactions (5.6% versus 18.8%) were more frequent in patients treated with carboplatin and paclitaxel. The allergic/hypersensitivity reactions were mainly secondary to carboplatin administration and was the reason for significantly lower rates of early discontinuation of one or both drugs in the paclitaxel arm compared with the PLD arm (1% versus 6%; p > 0.001). Fewer patients discontinued treatment early for toxicity in the carboplatin/PLD arm (6% versus 15%; p < 0.001).

Regarding hematologic toxicities, they were generally similar between the treatment groups, although grades 3 to 4 neutropenia was more frequent in patients treated with carboplatin/paclitaxel (35.2% versus 45.7%) and grades 3 to 4 thrombocytopenia was more frequent in patients treated with carboplatin/PLD (15.9% versus 6.2%). There were no differences in febrile neutropenia or the use of supportive treatment (e.g., transfusion, granulocyte colony-stimulating factor).

Recently, data on the final OS were reported. With a median follow-up of 49 months, no statistically significant difference in OS was observed between the two arms (HR: 0.99; 95% CI: 0.85 - 1.16; p = 0.94). The median OS was 30.7 months in patients treated with carboplatin and PLD and 33.0 months for patients treated with carboplatin and paclitaxel. The authors rationalize this fact with an imbalanced post-study cross-over between arms, with a greater proportion of patients randomized to carboplatin/paclitaxel receiving post-study PLD (68%) than patients in the carboplatin/PLD arm receiving post-study paclitaxel (43%; p < 0.001) [23].

The improved disease-related outcomes achieved with carboplatin/PLD treatment were not at the expense of quality of life [24].

This study provides an optional scheme of treatment for patients with platinum-sensitive ovarian cancer, with a reduction in severe toxicities, including carboplatin hypersensitivity reactions and peripheral neurotoxicity, both of which can be a reason for limiting the dose. Carboplatin/PLD also induced far less alopecia, one of the most feared adverse effects of chemotherapy for the majority of women.

4.4. Carboplatin/gemcitabine versus carboplatin/gemcitabine/bevacizumab (OCEANS)

In ovarian cancer, as in other tumors, the addition of new treatments is required for improved outcomes.

In a phase III clinical trial, 484 patients with relapsed platinum-sensitive ovarian cancer were randomly assigned to receive Carboplatin AUC 4 on day 1 and Gemcitabine 1000 mg/m^2 on days 1 and 8, every 21 days with placebo, or bevacizumab 15 mg/kg on day 1, every 21 days [25]. After 6 to 10 cycles of chemotherapy, bevacizumab or placebo were continued until toxicity or progression. The primary endpoint was progression-free survival, and secondary endpoints were overall response rate, overall survival and the duration of response.

With a median follow-up of 24 months, the analysis showed an increase in PFS (12.4 versus 8.4 months with a HR of 0.484; 95% CI 0.388 to 0.605; $p < 0.0001$) and in the RR (78.5% versus 57.4%, $p < 0.0001$) for bevacizumab. The duration of response was also significantly increased with the addition of bevacizumab (10.4 versus 7.4 months; HR: 0.534; 95% CI: 0.408 - 0.698). With the number of events for the final analysis not yet reached, the OS was 35.2 months in the placebo arm versus 33.3 months in the bevacizumab arm. This could be related to subsequent therapy, including patients receiving bevacizumab in the placebo arm (31%).

The bevacizumab arm had a higher incidence of grade 3 or higher hypertension (17.4% versus 1%) and proteinuria (8.5% versus <1%). There was no gastrointestinal perforation in any group.

This is the first positive phase III trial evaluating the addition of a targeting therapy to a standard platinum-based chemotherapy regimen for recurrent ovarian cancer.

4.5. New perspectives in the treatment of platinum-sensitive disease

The poly (adenosine diphosphate [ADP]-ribose) polymerases (PARPs) are a family of enzymes that play a role in the repair of DNA damage by repairing base excisions. The tumor-suppressor proteins BRCA1 and BRCA2 are components of the DNA repair pathway, and it is known that a germ-line mutation in BRCA1 or BRCA2 is associated with a high risk of the development of some cancers, including breast, prostate and ovarian cancer. Olaparib (AZD2281) is an oral PARP inhibitor that has shown activity in cancers associated with BRCA1 or BRCA2 mutations with an acceptable side-effect profile [26].

A randomized phase II clinical trial was designed to compare the efficacy of olaparib and PLD in patients with confirmed germ-line BRCA1 or BRCA2 mutations and recurrent or progressed ovarian cancer within 12 months of the most recent platinum-based chemotherapy regimen [27]. The primary endpoint was the progression-free survival by RECIST criteria, and secon-

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dary endpoints included the overall response rate, duration of treatment response, overall survival, safety and tolerability, and health-related quality of life. Ninety-seven patients were randomly assigned (1:1:1 ratio) to receive olaparib 200 mg twice per day, 400 mg twice per day continuously or PLD 50 mg/m^2 every 28 days. Patients were stratified by BRCA1 or BRCA2 status and platinum sensitivity (sensitive or resistant). There was no statistically significant difference in PFS between the olaparib 200 mg, olaparib 400 mg and PLD groups (6.5 months, 8.8 months and 7.1 months, respectively). The overall response rate was 25%, 31% and 18%, respectively, with no statistically significant difference. A similar duration of response was also observed (6.0, 6.8 and 5.5 months). There was no difference among groups in the OS or the health-related quality of life. Nausea, vomiting, fatigue and anemia were the most common adverse events related to olaparib; the adverse events related to PLD were stomatitis and palmo-plantar erythrodysesthesia.

In a second randomized phase II study, olaparib was evaluated in the maintenance treatment for patients with platinum-sensitive relapsed high-grade (grades 2 or 3) ovarian cancer who responded to their most recent platinum-based chemotherapy [28]. A total of 265 patients were randomized to receive olaparib 400 mg twice daily or placebo after completion of their last dose of platinum-based chemotherapy. The primary endpoint was progression-free survival; it was significantly longer in the olaparib group (8.4 months) than in the placebo group (4.8 months), with a hazard ratio for progression or death of 0.35 (95% CI 0.25 to 0.49; $p < 0.001$). Secondary efficacy endpoints were time to progression, objective response rate and overall survival. The time to progression was also significantly longer in patients treated with olaparib (8.3 versus 3.7 months; HR: 0.35; 95% CI 0.25 to 0.47; $p < 0.001$). According to the RECIST criteria, there was no difference in the response rate (12% versus 4%; $p = 0.12$) or in the overall survival in the interim analysis at 38% maturity (29.7 versus 29.9 months; $p = 0.75$). Nausea, vomiting, fatigue and anemia were the adverse events, with an incidence of at least 10% or higher in the olaparib group; the majority of them were grade 1 or 2.

The results of these two trials underline the necessity of further exploring the role of olaparib and other PARP inhibitors in the treatment of women with recurrent ovarian cancer. It may well be that their use has to be restricted to BRCA mutated patients, but a better definition of BRCAness should then be standardized. [29]

5. Treatment of platinum-resistant disease

Patients with platinum-resistant disease have a worse prognosis than patients with platinum-sensitive disease and a poorer response rate to cytostatic treatment. Although there is no clear recommendation for the standard treatment in these patients, there is a long list of drugs that have shown activity in phase II clinical trials in this situation: pegylated liposomal doxorubicin, topotecan, gemcitabine, paclitaxel, docetaxel, trabectedin, vinorelbine, ifosfamide, etoposide, and pemetrexed (Table 2).

Drug	Response rate	Main toxicity
Pegylated liposomal doxorubicin	20%	Hand-foot syndrome, mucositis
Topotecan	6 - 20%	Hematologic, alopecia
Gemcitabine	9 - 16%	Hematologic
Paclitaxel	13 - 17%	Neurotoxicity, alopecia
Docetaxel	23%	Hematologic
Trabectedin	6%	Hematologic
Vinorelbine	3 - 21%	Neutropenia
Ifosfamide	12%	Hematologic, central nervous toxicity
Etoposide	27%	Neutropenia
Pemetrexed	9 - 21%	Neutropenia, asthenia

Table 2. Response rate and toxicity for platinum-resistant disease

The comparisons between some of these drugs in phase III clinical trials do not yield superior results for any of the drugs in terms of overall or progression-free survival.

As explained, the response rate to platinum compounds is too low in patients with platinum-resistant disease, so monotherapy with a non-platinum drug is usually preferred because studies with doublets have not demonstrated superiority in platinum-resistant patients or either have presented greater toxicity [30 - 37].

Despite its frequent use in clinical practice, endocrine treatment (e.g., Tamoxifen, Letrozole) is not approved, and there is no good evidence supporting its use. Data on tamoxifen were obtained from observational studies, not comparative ones, and do not allow us to make any evidence-based recommendations [38]. In a phase II trial with letrozol carried out in 44 patients (half of them with platinum-resistant disease) who had primary tumors that expressed the estrogen receptor, a 9% overall response and 42% stabilization at 12 weeks was obtained in 33 patients with radiologically measurable disease, with a minimal toxicity [39]. In any case, there are worse data in the literature on the impact of endocrine therapy versus chemotherapy on progression-free survival [40]. Unfortunately, there are no phase III trials to make any recommendations about the use of hormone treatment in relapsed ovarian cancer.

The main phase III clinical trials comparing different agents in platinum-resistant relapsed ovarian cancer are shown below.

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5.1. Topotecan versus paclitaxel

Topotecan and paclitaxel are active in platinum-resistant relapsed ovarian cancer. To compare the activity of these two drugs in this setting, a phase III clinical trial was conducted in patients who had progressed during or after platinum-based therapy [41, 42]. A total of 226 patients were randomized to receive chemotherapy with topotecan 1.5 mg/m^2/24 h on 5 consecutive days, every 21 days (112 patients), or paclitaxel 175 mg/m^2, every 21 days (114 patients). The duration of treatment was dependent on response. Patients with a complete or partial response continued treatment until progression or for 6 months past the maximal response. Patients who progressed were removed from the study and patients with stable disease after six courses were removed from the study or switched to the alternate regimen (the study allowed crossover of the arms). None of the patients had previously received topotecan or paclitaxel (not included in standard first-line therapy as of now). Patients were stratified as platinum-resistant or as early, interim and late relapse groups. In the study, 53% of the patients did not respond to platinum-based treatment or had progression within 6 months; they had platinum-resistant disease (55% in the topotecan group and 52% in the paclitaxel group).

The primary efficacy parameters were the response rate, duration of response and time to progression. The secondary criteria for efficacy were the time to response and survival.

In the whole group of patients in the study, no differences in the response rates (topotecan 20.5% versus paclitaxel 13.2%; $p = 0.138$) or in the median survival (63 weeks for topotecan versus 53 weeks for paclitaxel, $p = 0.44$) were achieved. The duration of response was 32.1 weeks in patients treated with topotecan and 19.7 weeks in patients treated with paclitaxel ($p = 0.222$). There was no statistically significant difference in the time to progression after therapy (18.9 weeks for topotecan versus 14.7 weeks for paclitaxel; $p = 0.08$). The median time to documented radiologic response was inferior in the paclitaxel group (6 weeks) than in the topotecan group (9 weeks; $p = 0.041$).

Among platinum-resistant patients, the response rates were superior in the topotecan group than in the paclitaxel group (13.1 versus 6.7%, $p = 0.303$), and the median overall survival was 28.4 weeks in the topotecan group and 39.7 weeks in patients treated with paclitaxel.

Patients who had no ascites, better performance status and a smaller tumor burden had higher response rates.

The results of questionnaires on the quality of life, including pain, anorexia, diarrhea, fatigue, nausea and vomiting, dyspnea, constipation and insomnia, were similar in both groups.

Different toxicities were observed in the two groups. Hematologic toxicity was more frequent in the topotecan group, including grade 4 neutropenia (79% versus 23% in paclitaxel group; $p < 0.01$) and grade 4 thrombocytopenia (25% versus 2% in paclitaxel group; $p < 0.01$). Other toxicities more frequent in patients treated with topotecan were fatigue, nausea and vomiting (generally grades 1 – 2). Patients in the paclitaxel group experienced more alopecia, arthralgia, myalgia and neurotoxicity.

Patients who received topotecan after paclitaxel in their third-line treatment had an overall response rate of 13%, compared to 10% ($p = 0.638$) in patients who received paclitaxel after

topotecan. The data analysis for those patients receiving the other drug (paclitaxel or topotecan) in the third-line therapy showed that there was a degree of non-cross-resistance between them [43]. Therefore, the use of paclitaxel in first-line therapy does not prevent the administration of topotecan in relapsed epithelial ovarian cancer.

5.2. Paclitaxel versus pegylated liposomal doxorubicin

One study compared PLD 50 mg/m^2 every 4 weeks versus paclitaxel 175 mg/m^2 every 3 weeks in 214 patients with relapsed epithelial ovarian cancer [44].

There were no differences in the response rates among patients who received pegylated liposomal doxorubicin and patients who received paclitaxel (17.8% versus 22.4%; p = 0.034). There was also no difference in the PFS (21.7 weeks versus 22.4 weeks; p = 0.15) or OS (45.7 weeks versus 56.1 weeks; p = 0.44).

There were no observed differences in the PFS or OS in platinum-resistant or platinum-sensitive patients.

In the PLD group, hand-foot syndrome, stomatitis, nausea, and vomiting were more frequent. Conversely, alopecia, myalgia, arthralgia, and paresthesia were more frequent in the paclitaxel group.

5.3. Pegylated liposomal doxorubicin versus topotecan

To compare the efficacy and safety of PLD and topotecan in relapsed ovarian cancer after chemotherapy with platinum and taxanes, a phase III clinical trial was carried out in 474 patients [45, 46].

Patients were randomized to receive treatment with PLD 50 mg/m^2 every 28 days (239 patients), or topotecan 1.5 mg/m^2/24 h on 5 consecutive days, every 21 days (235 patients). The primary endpoint was time to progression, and the secondary endpoints included overall survival, response rate, time to response, duration of response and toxicity. The trial included 54% of the platinum-resistant patients in the PLD group and 53% of such patients in the topotecan group.

There was no difference in the rate of response between the two groups (19.7% in patients treated with PLD versus 17% in patients treated with topotecan; p = 0.390). A reduction in the risk of death by 18% was achieved in the group of patients treated with PLD compared to topotecan (HR = 1.216: 95% CI 1.000 to 1.478, p = 0.050). The median survival was 62.7 weeks in the PLD group versus 59.7 weeks in the topotecan group.

In the platinum-sensitive population, there were benefits in survival among patients treated with PLD, with a reduced risk of death by 30% (HR 1.432, 95% CI 1.066 to 1.923, p = 0.017) and a median survival of 107.9 weeks in the PLD group compared to 70.1 weeks in the topotecan group. The progression-free survival was 28.9 weeks for the PLD group and 23.3 weeks for the topotecan group (p =0.037), although the response rate was similar between the two groups (28.4% in the PLD group versus 28.8% in the topotecan group, p = 0.964).

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In the subgroup of platinum-resistant patients, (54% of the population of the study; 255 patients) there were no statistically significant differences in the response rate (12.3% for PLD and 6.5% for topotecan, p = 0.118), the PFS (9.1 weeks in patients who received PLD compared to 13.6 weeks in the topotecan group, p = 0.733), or OS (35.6 weeks for the PLD group and 41.3 for the topotecan group, p = 0.455, with a HR = 1.069, 95% CI 0.823 to 1.387, p = 0.618).

The toxicity profiles of the two drugs were different. The main toxicities in patients treated with PLD were hand-foot syndrome (49%) and stomatitis (40%). The main toxicities in patients treated with topotecan were hematological toxicity, so they were more likely to receive granulocyte colony-stimulating factor (29.1%), erythropoietin (23.1%) and transfusions (57.8%). Moreover, the toxicity caused by PLD was usually mild to moderate, while the toxicity caused by topotecan was more severe. Despite this difference, there was no difference in the health-related quality of life questionnaire at 12 weeks.

5.4. Gemcitabine versus pegylated liposomal doxorubicin

Two randomized phase III trials compared gemcitabine with PLD in patients with platinum-resistant disease.

The first trial [47] was carried out in 195 patients with platinum-resistant ovarian cancer who were randomly assigned to receive gemcitabine 1000 mg/m^2 on days 1 and 8, every 21 days, or PLD 50 mg/m^2 every 28 days until the progression of disease or unacceptable toxicity. Cross-over treatment was administered at progression. The primary endpoint was progression-free survival, and secondary endpoints were response rate, time to treatment failure, survival and quality of life.

The response rate was similar in both groups (9.2% for gemcitabine versus 11.7% for PLD, p = 0.772). There was no difference in the progression-free survival between patients treated with gemcitabine and patients treated with PLD (3.6 months versus 3.1 months, p = 0.870). The overall survival was similar in patients treated with gemcitabine followed by PLD and patients who received the inverse sequence (12.7 months versus 13.5 months, p = 0.997).

The toxicity profiles were different, with more hand-foot syndrome and stomatitis in the PLD arm and increased constipation, nausea and vomiting, fatigue and neutropenia in the gemcitabine arm. During the cross-over treatment, toxicity was similar to those observed during the initial treatment phase.

In a second study [48], 153 patients previously treated with platinum/paclitaxel who had relapsed or progressed within 12 months (53% within 6 months) were randomized to receive gemcitabine 1000 mg/m^2 on days 1, 8 and 15, every 28 days, or PLD 40 mg/m^2 every 28 days.

There were no differences in the response rate (29% for gemcitabine versus 16% for PLD, p = 0.066) or time to progression (20 weeks in gemcitabine group versus 16 weeks in PLD group, p = 0.411). Although the overall survival was higher in the PLD arm (51 weeks versus 56 weeks, p = 0.048), this difference was not detected in the platinum-resistant subgroup (relapse or progression < 6 months). The toxicity profile was similar to the previous study. Health-related quality of life favored the PLD arm.

5.5. Canfosfamide versus pegylated liposomal doxorubicin or topotecan

A phase III clinical trial (ASSIST-1) was designed to attempt to demonstrate superiority in the overall survival (primary endpoint) and progression-free survival (secondary endpoint) with canfosfamide versus PLD or topotecan in patients who progressed despite second-line treatment with either topotecan or PLD in platinum-refractory or -resistant patients [49].

The study included 461 patients randomized to an active control arm (PLD 50 mg/m^2 every 28 days or topotecan 1.5 mg/m^2 on days 1 – 5, every 21 days, based on the prior therapy) or canfosfamide 1000 mg/m^2 every 21 days.

The median overall survival was 8.5 months with canfosfamide and 13.5 months in the control arm ($p < 0.01$). The median OS was similar between PLD and topotecan (14.2 versus 10.8 months; $p = 0.1695$). The progression-free survival was longer for patients treated in the control group than for patients in the canfosfamide group (4.3 versus 2.3 months; $p < 0.01$). Hematologic adverse events were more frequent in the control arm, and non-hematologic adverse events were similar in both arms.

6. Extending the platinum-free interval

The cells of ovarian cancer could have intrinsic or acquired resistance to platinum compounds, which is a large clinical obstacle in the treatment of women with relapsed ovarian cancer. There are several mechanisms by which tumor cells can develop resistance to platinum, including increased efflux, enhanced DNA repair of damage caused by chemotherapy and defective cell death pathways. Some of these mechanisms may be reversible with time. It has been hypothesized that artificially extending the platinum-free interval with non-cross-resistant chemotherapy may improve the likelihood of responding to platinum salts subsequently administered and prolong the overall survival [35, 50, 51].

Recently, the OVA-301 trial [35] randomized 672 women with recurrent ovarian cancer to receive trabectedin 1.1 mg/m^2 plus PLD 30 mg/m^2 every 21 days, or PLD 50 mg/m^2 every 28 days. The primary endpoint was progression-free survival, and secondary endpoints included overall survival and safety. The PFS was higher in the combination group in the overall population of the study (7.3 versus 5.8 months; HR = 0.79, p = 0.0190) and in the platinum-sensitive patients (9.2 versus 7.5 months; HR = 0.73, p = 0.0170). The most common adverse effects were hand-foot syndrome in the PLD group and neutropenia and a transient ALT increase in the PLD/trabectedin group. After a median follow-up of 47.4 months, no difference in overall survival was observed (22.2 months in the combination group versus 18.9 months in the PLD group; HR = 0.86, p = 0.0835). Despite stratification based on platinum sensitivity, the authors detected an imbalance in the mean platinum-free interval, which favored the PLD group (13.3 versus 10.6 months; p = 0.009) [36].

Furthermore, the data reported in patients with a platinum-free interval of 6 - 12 months are especially interesting. These are the patients who can obtain the most benefit from an extension

in the platinum-free interval. In this population, the median PFS was 7.4 months in the PLD/trabectedin group versus 5.5 months in the PLD group (HR = 0.65; p = 0.0152) [52]. The median OS was 22.4 months in the PLD/trabectedin group versus 16.4 months in the monotherapy arm (HR = 0.64; p = 0.0027) [36].

In the OVA-301 study, similar proportions of patients received subsequent therapy in each arm (77% and 76%), with 56% and 57% receiving platinum-based therapies in the 6 - 12 months subgroup. In this subgroup, the time from randomization to subsequent platinum-based therapy was significantly longer for patients treated with PLD/trabectedin (9.8 versus 7.9 months; p = 0.0167). Patients randomized to the combination group experienced significantly longer survival after the initiation of subsequent platinum-based therapy (13.3 versus 9.8 months; HR = 0.63, p = 0.0357) [52]. These data support the hypothesis that the enhanced survival benefits may be due to an artificial extension of the platinum-free interval. In any case, this hypothesis should be confirmed in prospective randomized trials.

When the data on patients who received platinum-based therapy as the first subsequent treatment after PLD/trabectedin or PLD in the 6 - 12 months subset were analyzed, platinum was delayed 4 months (11.5 versus 7.5 months; HR: 0.61, p = 0.0203) and the overall survival from the first platinum treatment was significantly extended by a median of 8.7 months (18.6 versus 9.9 months; HR = 0.54, p = 0.0169) [53].

The delay in platinum re-treatment could promote the recovery from toxicities, such as polyneuropathy or alopecia.

7. Discussion

As previously shown, a longer platinum-free interval is the most important factor associated with a higher likelihood of response and prolongation of progression-free survival. Therefore, patients who relapse after six months of completion of chemotherapy and are responders are candidates for re-treatment with platinum salts.

The considerations in the choice of a second and subsequent line of chemotherapy in recurrent ovarian cancer may also include assessment of efficacy, cumulative toxicities and the optimal sequencing of available agents.

Currently, in patients with platinum-sensitive disease, it is preferred to administer a combination regimen including a platinum compound and a second active drug (Table 3). The platinum compound most commonly used is carboplatin, due to its better toxicity profile. These treatments provide a high response rate and significant improvements in the quality of life and progression-free survival compared to platinum monotherapy. However, the ideal platinum combination is unknown, and several regimens are available. Recently, schemes without platinum, such as PLD/trabectedin, have been developed and can be useful. Nevertheless, there are no data comparing these regimens to platinum-based schemes, so we must be prudent.

Clinical Trial	Scheme	Patients	RR	PFS	OS
ICON4/AGO-OVAR 2.2 [20]	C vs. C/P	n = 802	54% vs. 66%	9 vs. 12 m	24 vs. 29 m
AGO-OVAR 2.5 [24]	C vs. C/Gem	n = 356	30.9 vs. 47.2%	5.8 vs. 8.6 m	18 vs. 17.3 m
CALYPSO [25]	C/P vs. C/PLD	n = 976	Not achieved	9.4 vs. 11.3 m	33 vs. 30.7 m
OCEANS [28]	C/Gem/Pl vs. C/Gem/Bev	n = 484	57.4% vs. 78.5%	8.4 vs. 12.4 m	35.2 vs. 33.3 m

Abbreviations: RR: response rate. PFS: progression-free survival. OS: overall survival. C: carboplatin. P: paclitaxel. Gem: gemcitabine. PLD: pegylated liposomal doxorubicin, m: months.

Table 3. Main phase III clinical trials in platinum-sensitive relapsed ovarian cancer

The ICON4/AGO-OVAR 2.2 trial was the first clinical trial that showed the superiority of polychemotherapy to monotherapy in patients with platinum-sensitive relapsed ovarian cancer. The combination of carboplatin and paclitaxel may be used in patients who have no residual neurotoxicity, especially if the platinum-free interval is greater than one year.

A valid alternative is the administration of carboplatin plus PLD (CALYPSO), which has demonstrated similar efficacy to carboplatin/paclitaxel and a more favorable toxicity profile, with less alopecia, neurotoxicity and allergic/hypersensitivity reactions. Perhaps this is the most commonly used scheme by oncologists worldwide, now conditioned by a globally limited availability of PLD.

Although no survival benefit was achieved in the AGO-OVAR 2.5 trial with carboplatin and gemcitabine, the results of this clinical trial allow us to recommend this chemotherapy scheme as an alternative to carboplatin/paclitaxel, due to its different, and perhaps more favorable, toxicity profile. This scheme is especially useful for patients with risk factors for neurotoxicity development. The addition of an anti-angiogenic drug, such as bevacizumab (OCEANS), can improve outcomes without a significant increase in toxicity.

The incorporation of new active drugs into the treatment of patients with platinum-sensitive ovarian cancer is also important. Thus, we must be aware of the results of the phase III clinical trial, HECTOR (ClinicalTrials.gov Identifier: NCT00437307), which compares the combination of carboplatin plus topotecan with the current standard of care (carboplatin/paclitaxel, carboplatin/gemcitabine or carboplatin/PLD). The trial may be completed in 2013.

Because the response rate to platinum salts is too low in patients with platinum-resistant disease, monotherapy with a non-platinum drug is usually the choice in this setting. Comparisons of the efficacy of different active drugs in phase III clinical trials show no superiority of any of them, and there is no clear recommendation for the standard treatment in these patients. Therefore, the selection of treatment for platinum-resistant patients will be based on other criteria, such as toxicity, patient preferences and physician experience. Whenever possible, patients with platinum-resistant disease should be considered for treatment in clinical trials.

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Recurrent platinum-resistant ovarian cancer has limited treatment options and is generally treated sequentially with multiple single-agent regimens consisting of non-platinum and non-taxane chemotherapy.

The most common options are PLD, topotecan and gemcitabine. These options have been compared in several phase III clinical trials (Table 4), but none of the options have proven superior. PLD and gemcitabine could be used in patients who do not desire alopecia. Additionally, PLD is dosed less frequently than topotecan and gemcitabine, which results in improved convenience for the patient and a reduction in the use of resources.

Subsequent lines of treatment will be made with available drugs.

Author, year	Drugs	Patients	RR	PFS	OS
ten Bokkel Huinink W, 2004	Topotecan vs. Paclitaxel	n = 226	13.1% vs. 6.7%**	23.1 vs. 14 w*	28.4 vs. 39.7 w**
O'Byrne KJ, 2002	Paclitaxel vs. PLD	n = 214	22.4% vs. 17.8%*	22.4 vs. 21.7 w*	56.1 vs. 45.7 w*
Gordon AN, 2004	PLD vs. Topotecan	n = 474	12.3% vs. 6.5%**	9.1 vs. 13.6 w**	35.6 vs. 41.3 w**
Mutch DG, 2007	Gemcitabine vs. PLD	n = 195	9.2% vs. 11.7%**	3.6 vs. 3.1 m**	12.7 vs. 13.5 m**
Ferrandina G, 2008	Gemcitabine vs. PLD	n = 153	29% vs. 16%*	20 vs. 16 w*	51 vs. 56 w*

*Data from the whole group

**Data from platinum-resistant patients

Abbreviations: RR: response rate, PFS: progression-free survival, OS: overall survival, PLD: pegylated liposomal doxorubicin, w: weeks, m: months.

Table 4. Main phase III clinical trials including platinum-resistant relapsed ovarian cancer

Recently, the use of non-platinum agents in relapsed ovarian cancer to extend the platinum-free interval has gained interest. The answer to the question of whether the prolongation of the platinum-free interval increases overall survival after the reintroduction of platinum should be revealed by two phase III trials currently in progress. The MITO-8 (ClinicalTrials.gov Identifier: NCT00657878) trial compares carboplatin/paclitaxel followed by PLD versus the reverse sequence (PLD followed by carboplatin/paclitaxel), and the INOVATYON trial (ClinicalTrial.gov identifier: NCT01379989) compares the administration of carboplatin/PLD followed by treatment at the discretion of the investigator versus PLD/trabectedin followed by a platinum-based.

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