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Efficacy, Safety, and Prognosis of Current Phase III Chemotherapy for Platinum-Resistant Ovarian Cancer: A Systematic Review

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ABSTRACT: Platinum-resistant ovarian cancer is associated with poor prognosis, and chemotherapy remains widely used despite modest efficacy. This systematic review evaluated the efficacy and safety of chemotherapy in platinum-resistant ovarian cancer using phase III randomized trials. The review followed PRISMA 2020 guidelines and was registered in PROSPERO (CRD42024593673). PubMed, Embase, ScienceDirect, and the Cochrane Central Register of Controlled Trials were searched for phase III randomized trials investigating chemotherapy in recurrent platinum-resistant ovarian cancer. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool. Three phase III randomized trials met the inclusion criteria. Median progression-free survival ranged from approximately 3 to 8 months, while no consistent overall survival benefit was observed across chemotherapy strategies. Combination regimens increased objective response rates. Dose modification and alternative scheduling maintained comparable efficacy while improving tolerability, whereas novel cytotoxic agents did not demonstrate superiority over standard chemotherapy. All included studies raised some risk-of-bias concerns, primarily because of open-label designs. Overall, the evidence indicates that cytotoxic chemotherapy offers modest, short-lived clinical benefit, with limited impact on overall survival. Dose-optimized pegylated liposomal doxorubicin (40 mg/m²) appears practical, as it preserves efficacy while improving tolerability. Lurbinectedin has not demonstrated improved outcomes in this patient population. Although trabectedin plus pegylated liposomal doxorubicin may improve response rates and prolong progression-free survival, additional toxicity and the absence of an overall survival benefit restrict its use to selected patients. Therefore, chemotherapy should primarily support symptom control and short-term disease stabilization. Future improvements will likely depend on biomarker-guided targeted strategies.

1. INTRODUCTION

Ovarian cancer remains a major challenge in gynecologic oncology, particularly in the setting of platinum-resistant disease, which is associated with poor survival and limited therapeutic options (Havasi et al., 2023). Approximately 25% of patients treated with platinum-based regimens eventually develop resistance (Atallah et al., 2023), with a median overall survival of 9–

12 months and progression-free survival of 3–4 months (Li et al., 2023; Marchetti et al., 2021). Given this poor prognosis and the lack of a clearly superior standard, defining the best evidence-based treatment approach is an urgent clinical priority.

In this context, systemic chemotherapy continues to play a central role, despite modest response rates of 10–30% (Li et al., 2023). Agents such as topotecan, lurbinectedin, paclitaxel, trabectedin, carboplatin, and pegylated liposomal doxorubicin (PLD) remain commonly used in routine clinical practice for platinum-resistant ovarian cancer (Gaillard et al., 2021; Clamp et al., 2022; Vergote et al., 2020; Monk et al., 2020; Motohashi et al., 2021). At the same time, the therapeutic landscape has expanded to include targeted therapies and immunotherapies, which warrant examination of how far they have actually shifted practice. Beyond therapeutic developments, advances in artificial intelligence have also contributed to cancer detection and classification, highlighting the growing role of technology in supporting oncological decision-making (Doni et al., 2025).

Poly-ADP-ribose polymerase inhibitors have demonstrated efficacy primarily in patients with BRCA1 or BRCA2 mutations, yet progression-free survival is often comparable to chemotherapy, with increased toxicity and uncertain long-term benefit (Nicum et al., 2024; Kristeleit et al., 2022; Yang et al., 2020). Importantly, resistance to PARP inhibitors has been associated with reduced sensitivity to subsequent chemotherapy, complicating treatment sequencing (Frenel et al., 2022; Kristeleit & Moore, 2022). Other targeted agents, including mirvetuximab soravtansine, are restricted to biomarker-selected populations due to dependence on folate receptor alpha expression (Moore et al., 2021; Coleman et al., 2024). Immunotherapy strategies, either as monotherapy or in combination with CTLA-4 inhibitors, chemotherapy, PARP inhibitors, or anti-VEGF agents, have shown modest activity, with overall response rates ranging from 8% to 31.4% and median progression-free survival between 1.9 and 7.6 months in recurrent or platinum-resistant disease (Matulonis et al., 2019; Zamarin et al., 2020; Pujade-Lauraine et al., 2021; Lee et al., 2020; Liu et al., 2019; Zsiros et al., 2021). Notably, the MOONSTONE/GOG-3032 trial reported a low response rate and a high incidence of treatment-emergent adverse events with the niraparib-dostarlimab combination, raising concerns about tolerability and clinical applicability (Randall et al., 2023).

Despite these developments, several gaps remain. First, most recent trials and reviews have focused on novel targeted or immunotherapeutic agents. In contrast, chemotherapy, which remains the most widely used backbone in practice, is often treated only as a comparator rather than as the subject of appraisal. Second, evidence on individual cytotoxic agents is scattered across trials with heterogeneous designs, comparators, and endpoints, making it difficult for clinicians to directly compare regimens. Third, efficacy outcomes are frequently reported separately from safety and prognostic impact, so the trade-off between survival benefit and toxicity is rarely assessed in an integrated way.

This study differs from previous work by focusing exclusively on phase III chemotherapy trials in platinum-resistant ovarian cancer and by synthesizing efficacy, safety, and prognostic impact into a single framework. Restricting the analysis to phase III evidence offers a higher level of certainty than reviews that mix early-phase and non-randomized data, and it provides an updated benchmark against which emerging targeted and immunotherapeutic strategies can be judged.

Given these limitations and considerations of access and resource allocation, chemotherapy remains the most pragmatic treatment option for platinum-resistant ovarian cancer. This review, therefore, aims to appraise the efficacy, safety, and prognostic impact of chemotherapy regimens evaluated in phase III trials. Specifically, it addresses three questions: (1) What survival and response outcomes have been achieved with different chemotherapy regimens? (2) What is their toxicity profile? (3) Which factors influence prognosis in this population?

Theoretically, this work consolidates the phase III evidence base and clarifies the current role of chemotherapy relative to targeted and immune-based approaches. Methodologically, it offers a structured, integrated assessment of efficacy and safety outcomes. Practically, it supports clinical decision-making, particularly in settings where access to biomarker testing and novel agents is limited, and it can inform treatment guidelines and the design of future trials in platinum-resistant ovarian cancer.

2. MATERIALS AND METHODS

2.1 Protocol and Reporting Standards

This systematic literature review was conducted in accordance with the PRISMA 2020 guidelines [24] and registered in PROSPERO (CRD42024593673). The protocol was developed a priori to minimize bias and ensure methodological rigor. The research question was formulated using the Population–Intervention–Comparison–Outcomes–Time–Study (PICOTS) framework, which guided study selection, data extraction, and outcome assessment (Table 1).

Table 1. Characteristics of included studies

Study	Location	Participants	Interventions	Result
Monk study	USA Russian Australia Israel UK China South Africa New Zealand Poland Switzerland	576 women aged 18+ with advanced-relapsed epithelial ovarian cancer were randomly assigned 1:1 to intravenous infusions of either T+PLD or PLD	Intervention: PLD 30 mg/m2 for 1.5 hours followed by trabectedin 1.1 mg/ m2 for 3 hours every 3 weeks. Control: PLD 50 mg/m2 for 1.5 hours every 4 weeks	Primary endpoints: Median OS 23.8 months with T+PLD vs. 22.2 months with PLD (HR: 0.92, 95% CI:0.73–1.18; p=0.52). Secondary endpoints: Median PFS 7.52 vs. 7.26 months (HR: 0.93, 95% CI:0.76–1.15; p=0.52); ORR 46% vs. 35.9% (OR: 1.52, 95% CI: 1.07–2.16; p=0.01). Exploratory endpoints: Patients with BRCA1/2 mutations had a median PFS of 10.1 months with T+PLD vs. 7.6 months with PLD (HR: 0.72, 95% CI: 0.48-1.08; p=0.039). Patients with BRCA1/2 mutations and a 6–12 months PFI, median OS was 31.5 vs. 14.9 months (HR: 0.37, 95% CI: 0.17-0.82; p=0.011). Grade 3–4 AEs were higher in T+PLD (79%) vs. PLD (54%).
JCOG3018 trial	Japan	272 patients were randomly assigned 1:1 to two treatment regimens: experimental arm (n=137) and standard arm (n=135).	Experimental arm (40 mg/m2 PLD) or a standard arm (50 mg/m2 PLD) until 10 courses	Primary endpoint: In the experimental arm vs. standard arm, median PFS was 4.0 months in both arms (HR=1.065; 95% CI=0.830–1.366). Secondary endpoints: In the experimental arm vs. standard arm, median OS was 14.0 months in both arms (HR=1.078; 95% CI=0.831–1.397). The standard arm experienced more hematologic toxicity and oral cavity mucositis (grade 2) than the experimental arm, but the grade 2 hand-foot skin reaction remained unchanged.
CORAIL trial	Austria Belgium Bulgaria Czech Republic France	442 patients were randomly assigned (1:1) to receive either lurbinectedin or the control arm	Experimental arm: Lurbinectedin 3.2 mg/m2 1 hour i.v. infusion on day 1 every 3 weeks. Control arm:	With a median follow-up of 25.6 months, the median PFS was 3.5 months (95% CI, 2.1–3.7) in the lurbinectedin arm and 3.6 months (95% CI, 2.7–3.8) in the control arm (stratified log-rank p = 0.6294; HR = 1.057).

	Hungary Italy Romania Serbia Spain United Kingdom USA	(127 with PLD and 94 with topotecan).	PLD (50 mg/m2, 1 hour i.v. every 4 weeks) or topotecan (1.5 mg/m2, 30 minutes i.v. on days 1-5 every 3 weeks). Both arms received antiemetic prophylaxis (dexamethasone and ondansetron i.v. at least 8 mg or equivalent).	ORR according to RECIST v.1.1 by IRC was 14.5% (95% CI, 10.1–19.5 months) (lurbinectedin arm) and 12.7% (95% CI, 8.6–17.8 months) (control arm) (p = 0.6772) Grade ≥3 AEs were most frequently observed in the control arm: 64.8% vs. 47.9% (p = 0.0005). The most common grade ≥3 AEs in the lurbinectedin arm were fatigue (7.3%), nausea (5.9%), vomiting, and febrile neutropenia (5.5% each). The most common grade ≥3 AEs in the control arm were mucosal inflammation (8.5%), fatigue (8.0%), and palmar-plantar erythrodysesthesia syndrome (7.0%). Alopecia was observed in 1.6% (lurbinectedin arm) and 13.6% of patients (control arm). The most relevant grade ≥3 laboratory abnormalities in lurbinectedin vs. the control arm were neutropenia (32.0% vs. 41.4%), anemia (18.7% vs. 31.0%), thrombocytopenia (9.1% vs. 16.2%), and ALT increase (6.8% vs. 1.9%).

2.2 Eligibility Criteria

Eligible studies included patients with platinum-resistant recurrent ovarian cancer, defined as disease recurrence within six months after completion of platinum-based primary therapy. Interventions of interest comprised cytotoxic chemotherapy regimens administered as monotherapy or combination therapy, typically delivered over 6 cycles, with extension to 10 cycles in cases of documented clinical response. No direct comparator was required. Primary outcomes included treatment efficacy, safety, and progression-free survival, while prognostic outcomes were assessed using follow-up data up to 5 years, when available. Only randomized controlled trials, including phase III trials, were eligible.

2.3 Search Strategy

A comprehensive literature search was conducted in PubMed, Embase, ScienceDirect, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was developed based on the PICOTS framework and refined through pilot testing to optimize sensitivity and specificity. Controlled vocabulary and free-text terms related to ovarian cancer, platinum resistance, chemotherapy, and recurrent disease were combined. The core search string applied across databases was: "chemotherapy AND (platinum-resistant OR platinum refractory) AND recurrent ovarian cancer AND randomized trial." The search was limited to English-language publications, and no restrictions on publication year. Full search strategies are provided in (Supplementary Table 2).

Table 2. Search Strategy

No	Database	Keyword MeSH	Initial Results
1	Pubmed	(chemotherapy) AND (platinum) AND (resistant OR immune) AND (recurrent OR frequent OR intermittent) AND (ovarian OR ovary OR ovarium) AND (cancer OR carcinoma OR malignancy OR tumor)	265
2	ScienceDirect	chemotherapy AND platinum AND resistant AND recurrent ovarian cancer	7308
3	Cochrane Library	(chemotherapy) AND (platinum) AND (resistant OR immune) AND (recurrent OR frequent OR intermittent) AND (ovarian OR ovary OR ovarium) AND (cancer OR carcinoma OR malignancy OR tumor)	7

2.4 Study Selection

All retrieved records were imported into Mendeley Desktop for duplicate removal and reference management. Two reviewers independently screened titles and abstracts, followed by full-text assessment using predefined eligibility criteria. Disagreements were resolved by consensus. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

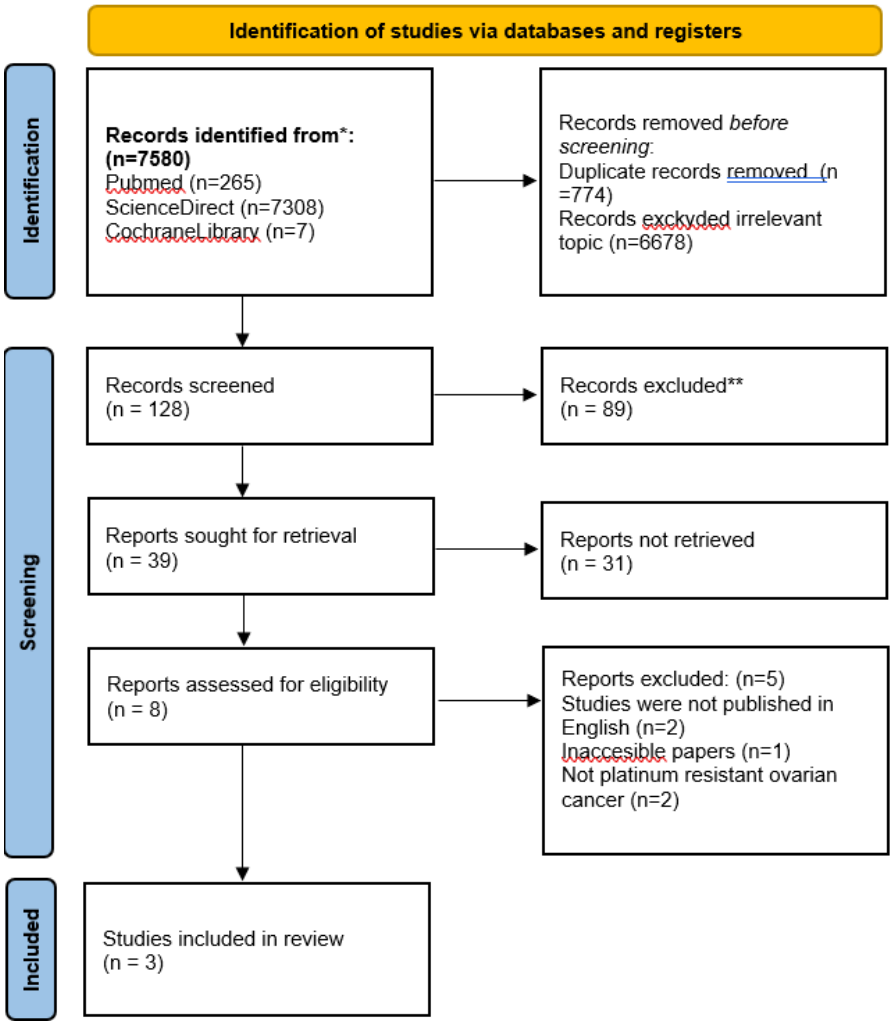


Fig 1. PRISMA flow of study selection

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2.5 Inclusion and Exclusion Criteria

Studies were included if they evaluated cytotoxic chemotherapy regimens in platinum-resistant or platinum-refractory recurrent ovarian cancer, reported efficacy and/or safety outcomes, employed randomized trial designs, and provided accessible full-text articles. Studies lacking full-text availability, relevant clinical outcomes, or sufficient methodological detail were excluded.

2.6 Data Extraction

Three reviewers independently extracted data using a standardized form. Extracted variables included study characteristics, patient population, chemotherapy regimens, treatment duration, efficacy outcomes, safety profiles, and survival data. Data were categorized according to predefined research questions addressing treatment efficacy, comparative outcomes, and adverse events.

2.7 Risk of Bias Assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2 (ROB 2) tool via the RevMan Web platform. Each study was evaluated across domains of randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Studies were classified as low risk, some concerns, or high risk of bias.

3. RESULTS AND DISCUSSION

3.1 Study Selection

The literature search identified 7,580 records from electronic databases, including PubMed (n = 265), ScienceDirect (n = 7,308), and the Cochrane Library (n = 7). After removal of duplicate records (n = 774) and records deemed irrelevant based on title and abstract screening (n = 6,678), 128 records remained for screening. Following title and abstract screening, 89 records were excluded. Full-text retrieval was attempted for 39 reports, of which 31 could not be retrieved. Eight full-text articles were assessed for eligibility. Of these, three studies were excluded due to publication in non-English languages (n = 2) or inaccessible full text (n = 1). Ultimately, five studies met the inclusion criteria and were included in the final qualitative synthesis. (Figure 1)

3.2 Quality Assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2 (ROB 2) tool across five domains for all included phase III randomized trials (Figure 2). Overall, all studies were judged to have some concerns for risk of bias, primarily driven by deviations from intended interventions and outcome measurement, while other domains were generally robust.

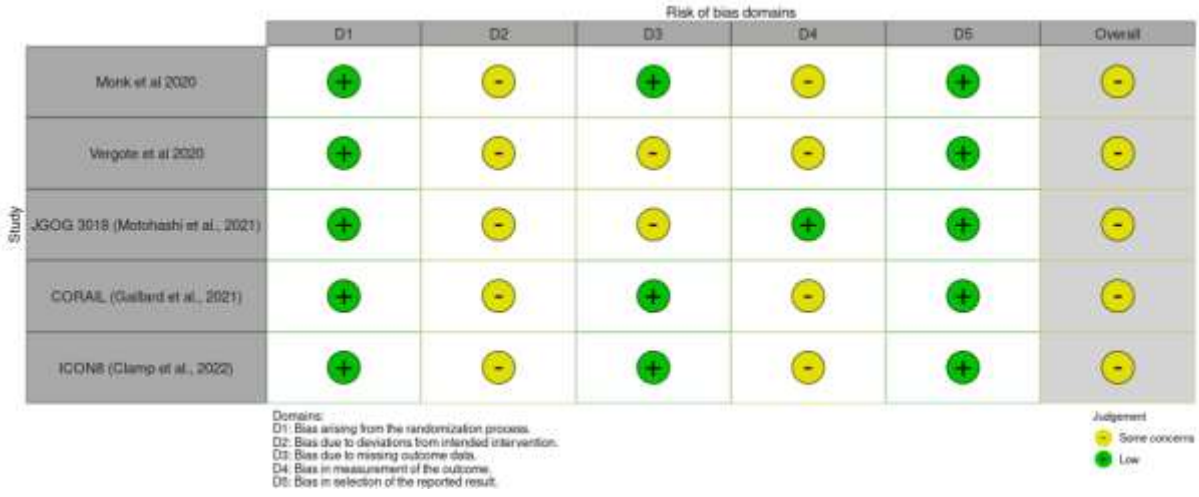


Fig 2. Risk of bias assessment of included studies

Bias arising from the randomization process (D1) was consistently assessed as low risk across all trials, reflecting adequate random sequence generation and balanced baseline characteristics. Bias due to deviations from intended interventions (D2) was judged to be of some concern across all studies, largely attributable to open-label designs and the potential for dose modification or differential supportive care.

Bias due to missing outcome data (D3) was predominantly assessed as low risk, with some concerns noted in selected trials due to early termination or analytical approaches relying on per-protocol populations. Bias in the measurement of outcomes (D4) was assessed as a concern in most studies, reflecting investigator-assessed progression-free survival and response outcomes in open-label settings. Bias in the selection of the reported result (D5) was uniformly assessed as low risk because the primary and secondary endpoints were prespecified and reported consistently with trial protocols.

3.3 Study Characteristics

Three phase III randomized controlled trials evaluating cytotoxic chemotherapy in platinum-resistant or platinum-relevant recurrent ovarian cancer were included in the final qualitative synthesis. Two trials specifically enrolled patients with platinum-resistant or platinum-refractory disease (CORAIL and JGOG 3018). In contrast, one recurrent ovarian cancer trial (trabectedin plus PLD) included prespecified platinum-resistant and short platinum-free interval subgroups. Across studies, patients were heavily pretreated, and primary endpoints included progression-free survival, overall survival, and treatment-related toxicity. (Table 1)

AEs: adverse effect, AUC: area under the curve, BRCA: BReast CAncer gene, CI: confidence intervals, Cr-EL: Cremophor-EL, ECOG: Eastern Cooperative Oncology Group, i.v: intravenous, IRC: Independent Review Committee, HR: hazard ratio, ORS: Objective response rate, OS: overall survival, PFI: platinum-free interval, PFS: progression free survival, PLD: pegylated liposomal doxorubicin, PP: per protocol, RCT: randomized controlled trial, RECIST: Response Criteria in Solid Tumors, T: trabectedin, UK: United Kingdom, USA: United States of America

3.4 Efficacy Across Chemotherapy Strategies

Across all included trials, median progression-free survival remained limited, generally ranging from 3 to 8 months, with no consistent improvement in overall survival across chemotherapy strategies. Combination chemotherapy, particularly trabectedin plus pegylated liposomal doxorubicin, resulted in higher objective response rates compared with single-agent therapy. However, these improvements did not translate into a statistically significant overall survival benefit in the overall study populations.

Dose modification and alternative scheduling strategies, including reduced-dose pegylated liposomal doxorubicin and weekly paclitaxel-based regimens, demonstrated efficacy comparable to standard dosing schedules. Similarly, novel cytotoxic agents such as lurbinectedin failed to show superiority over established chemotherapy options in terms of progression-free or overall survival.

3.5 Discordance Between Response and Survival

Despite higher objective response rates observed with certain combination regimens, improvements in response did not consistently correlate with prolonged survival. This discordance likely reflects the limited durability of tumor responses, rapid development of resistance, and the impact of subsequent lines of therapy, which may attenuate survival differences in heavily pretreated populations.

3.6 Toxicity and Treatment Burden

Treatment intensification through combination chemotherapy or novel agents was consistently associated with increased toxicity. Higher rates of grade ≥3 adverse events, particularly hematologic toxicity, were observed in intensified treatment arms. In contrast, dose-reduced or schedule-modified regimens achieved similar survival outcomes with improved tolerability, suggesting a more favorable balance between efficacy and treatment burden in this population.

3.7 Subgroup-Specific Signals

Exploratory subgroup analyses suggested potential benefit in selected patient populations. Patients with BRCA1/2 mutations or longer platinum-free intervals demonstrated improved progression-free and overall survival with certain combination regimens. However, these findings were derived from post hoc or exploratory analyses and were not consistently replicated across trials, limiting their generalizability.

3.8 Consistency of Phase III Outcomes

Across phase III trials, the absence of meaningful improvement in overall survival was consistent regardless of chemotherapy class, dosing strategy, or geographic region. This consistency across heterogeneous study designs suggests that the observed

lack of survival benefit reflects intrinsic limitations of cytotoxic chemotherapy in platinum-resistant ovarian cancer rather than trial-specific methodological factors.

3.9 Discussion

Platinum-resistant ovarian cancer (PROC) remains a major therapeutic challenge, characterized by aggressive tumor biology, rapid development of drug resistance, and poor survival outcomes. Contemporary evidence indicates that cytotoxic chemotherapy provides only modest and transient clinical benefit, with limited impact on long-term survival despite occasional improvements in tumor response (Havasi et al., 2023; Li et al., 2023).

3.9.1 Magnitude of Clinical Benefit of Chemotherapy in Platinum-Resistant Ovarian Cancer

Phase III evidence included in this review consistently demonstrates that chemotherapy in PROC yields low objective response rates (ORRs) and short progression-free survival (PFS) durations. The CORAIL phase III trial showed that lurbinectedin failed to improve outcomes compared with standard chemotherapy (pegylated liposomal doxorubicin or topotecan), with nearly identical median PFS (3.5 vs 3.6 months) and comparable ORR, confirming the limited efficacy of cytotoxic agents in this setting (Gaillard et al., 2021).

Similarly, the JGOG 3018 randomized phase III trial demonstrated no survival advantage between higher- and lower-dose pegylated liposomal doxorubicin in platinum-resistant and platinum-refractory ovarian cancer, with comparable PFS and overall survival (OS) across treatment arms (Motohashi et al., 2021). Systematic reviews and network meta-analyses further support these findings, reporting median PFS of approximately 3–4 months and median OS generally below 12 months for most chemotherapy regimens in PROC (Li et al., 2023).

Collectively, these data indicate that chemotherapy in PROC provides limited and short-lived disease control, functioning primarily as a palliative intervention rather than a disease-modifying strategy.

3.9.2 Why Higher Objective Response Rates Fail to Translate into Overall Survival Benefit

A consistent observation across studies included in this review is the lack of concordance between improvements in ORR and OS. Platinum resistance arises from complex biological mechanisms, including enhanced DNA damage repair, epigenetic alterations, and immune escape, leading to the rapid emergence of treatment-resistant tumor clones even after initial response (Havasi et al., 2023; Marchetti et al., 2021).

Furthermore, OS in PROC is strongly influenced by post-progression therapies, including subsequent chemotherapy, targeted agents, and supportive care, which attenuate survival differences between treatment arms (Li et al., 2023). As highlighted in recent meta-analyses, ORR and PFS function as imperfect surrogate endpoints for OS in recurrent ovarian cancer, particularly in platinum-resistant disease (Li et al., 2023).

3.9.3 Chemotherapy Intensification: Efficacy versus Toxicity

Evidence from trials included in this review does not support chemotherapy intensification to improve survival in PROC. Combination regimens may increase ORR, but these gains have not translated into OS benefit and are frequently accompanied by increased toxicity. The randomized phase III trial evaluating trabectedin combined with pegylated liposomal doxorubicin demonstrated higher response rates than pegylated liposomal doxorubicin alone, yet did not improve OS and was associated with higher rates of grade 3–4 adverse events (Monk et al., 2020).

In contrast, dose optimization strategies appear more clinically meaningful. The JGOG 3018 trial demonstrated that lower-dose pegylated liposomal doxorubicin achieved comparable efficacy with improved tolerability, supporting a strategy of toxicity minimization rather than dose escalation in PROC (Motohashi et al., 2021). These findings align with contemporary understanding that chemotherapy intensification primarily increases treatment burden without delivering durable clinical benefit (Havasi et al., 2023; Li et al., 2023; Marchetti et al., 2021).

3.9.4 Patient Subgroups with Potential Differential Benefit

Exploratory analyses suggest that certain patient subgroups may derive greater benefit from specific chemotherapy strategies. Patients with longer platinum-free intervals, better performance status, and preserved organ function may experience improved disease control and symptom relief (Li et al., 2023; Motohashi et al., 2021).

Post hoc analyses from the SOLO2/ENGOT Ov-21 trial indicate that patients with BRCA1/2-Mutant tumors may retain partial sensitivity to subsequent chemotherapy after progression on PARP inhibitors, although this observation remains hypothesis-generating in platinum-resistant populations (Frenel et al., 2022; Kristeleit & Moore, 2022). Similarly, results from ARIEL4 suggest differential outcomes based on BRCA mutation status when chemotherapy is compared with PARP inhibition, underscoring the biological heterogeneity of recurrent ovarian cancer (Kristeleit et al., 2022).

Importantly, these subgroup findings should be interpreted cautiously, as most trials were not powered to detect differential treatment effects across molecular or clinical strata.

3.9.5 Balancing Efficacy, Toxicity, and Quality of Life in Clinical Decision-Making

Given the limited survival benefit of chemotherapy in PROC, treatment decisions should prioritize net clinical benefit by integrating efficacy, toxicity, and quality-of-life considerations. Disease stabilization or modest tumor shrinkage may be clinically meaningful when accompanied by symptom improvement and acceptable toxicity.

Trials included in this review highlight that excessive toxicity may compromise quality of life without improving survival outcomes (Li et al., 2023; Motohashi et al., 2021). Therefore, regimens with comparable efficacy but improved tolerability should be preferred, and treatment goals should be clearly discussed with patients. In select clinical scenarios requiring rapid disease control, more aggressive regimens may be considered; however, patients should be counseled about the low likelihood of a survival benefit and the increased risk of adverse effects.

3.9.6 Most Promising Chemotherapy Regimen for Platinum-Resistant Recurrent Ovarian Cancer

Within the restricted phase III evidence base included in this review, no cytotoxic chemotherapy strategy has demonstrated a consistent overall survival advantage in an unselected PROC population; therefore, the most promising chemotherapy regimen should be defined by the most favorable balance of disease control, tolerability, and feasibility. Across the evaluated strategies, dose-optimized pegylated liposomal doxorubicin (PLD) is the most pragmatic option: in JGOG 3018, PLD 40 mg/m2 achieved identical median PFS and OS compared with PLD 50 mg/m2, while reducing clinically relevant toxicities (notably hematologic toxicity and oral mucositis), supporting lower-dose PLD when chemotherapy is chosen (Motohashi et al., 2021). Standard single-agent options such as PLD and topotecan remain appropriate references, as reflected in the physician-choice comparator in CORAIL and in contemporary RCT syntheses (Li et al., 2023; Gaillard et al., 2021). In contrast, substituting a novel cytotoxic agent (lurbinectedin) did not improve PFS or ORR over these standards in CORAIL (Gaillard et al., 2021). A combination approach (trabectedin plus PLD) increased ORR and modestly prolonged PFS but did not confer an OS benefit in the overall population and substantially increased grade 3-4 adverse events; moreover, the trial enrolled a mixed recurrent population, so generalizability to strictly PROC cohorts is limited, and any apparent benefit should be interpreted as exploratory (Monk et al., 2020).

3.9.7 Side Effects and Prognosis of Evaluated Chemotherapy Regimens

The included phase III trials provide regimen-specific toxicity patterns and prognosis estimates that directly inform clinical choice. For PLD, JGOG 3018 indicates that increasing the dose from 40 to 50 mg/m2 does not improve prognosis (median PFS 4.0 months and median OS 14.0 months in both arms) but increases treatment burden, including higher hematologic toxicity and oral mucositis; therefore, the lower dose offers a more favorable therapeutic index (Motohashi et al., 2021). In CORAIL, prognosis was similarly limited across arms (median PFS 3.5 months with lurbinectedin versus 3.6 months with PLD/topotecan, and ORR 14.5% versus 12.7%). However, toxicity profiles differed: lurbinectedin was more often associated with systemic symptoms and hematologic complications (e.g., fatigue, nausea/vomiting, and febrile neutropenia), whereas the control arm experienced higher overall grade >=3 adverse events and a distinct spectrum including mucosal inflammation and palmar-plantar erythrodysesthesia, as well as higher alopecia rates (Gaillard et al., 2021). For trabectedin plus PLD, the trial reported higher ORR and longer PFS compared with single-agent PLD, yet without a significant OS advantage in the overall population and with markedly higher grade 3-4 toxicity (79% versus 54%), indicating that any additional tumor control comes at a substantial safety cost (Monk et al., 2020). Mechanistic reviews suggest these clinical patterns are consistent with the biology of platinum resistance—rapid emergence of resistant clones and limited response durability—thereby constraining prognosis despite transient responses (Havasi et al., 2023; Marchetti et al., 2021).

3.9.8 Clinical Synthesis for Chemotherapy Selection in PROC

These findings support a patient-centered approach in which chemotherapy selection prioritizes symptom control and quality of life, selecting the least toxic regimen likely to provide clinically meaningful stabilization. For patients who are candidates for PLD, lower-dose PLD (40 mg/m2) is supported as an evidence-based option that avoids unnecessary toxicity without sacrificing efficacy (Motohashi et al., 2021). When PLD is contraindicated or has been exhausted, standard alternatives such as topotecan remain reasonable comparators, with the understanding that expected benefits are modest and treatment-related toxicity can be substantial (Li et al., 2023; Gaillard et al., 2021). Chemotherapy intensification should be reserved for carefully selected circumstances (e.g., urgent need for tumor shrinkage and adequate performance status), given the lack of consistent OS benefit and the higher rate of severe adverse events observed with combination cytotoxic therapy (Monk et al., 2020). Where available, enrollment in clinical trials and biomarker-directed approaches should be prioritized, as contemporary evidence suggests that overcoming platinum resistance is more likely to depend on targeted strategies than on further escalation of non-selected cytotoxic chemotherapy (Havasi et al., 2023; Li et al., 2023; Marchetti et al., 2021).

3.9.9 Strengths and Limitations

This review is strengthened by its exclusive focus on phase III randomized controlled trials, ensuring reliance on high-level clinical evidence. Strict population criteria were applied to maintain relevance to platinum-resistant or platinum-relevant recurrent ovarian cancer, and outcomes were assessed across efficacy, survival, and toxicity to provide a balanced evaluation of clinical benefit and treatment burden.

Limitations include the small number of eligible trials, which reflects the limited availability of randomized evidence in platinum-resistant ovarian cancer and precluded quantitative meta-analysis. Heterogeneity in patient populations, prior therapies, and chemotherapy regimens may limit cross-trial comparability. Subgroup findings, particularly those related to BRCA status and platinum-free interval, were exploratory and should be interpreted with caution. Most trials used open-label designs, which may introduce potential bias, although objective survival endpoints reduce this concern.

4. CONCLUSION

This review demonstrates that cytotoxic chemotherapy provides limited and short-lived clinical benefits in platinum-resistant ovarian cancer, without a consistent overall survival advantage in unselected populations. The principal finding is that dose-optimized pegylated liposomal doxorubicin (PLD) at 40 mg/m2 represents the most pragmatic chemotherapy option among the evaluated regimens, as it maintains comparable efficacy while reducing treatment-related toxicity compared with the higher dose. In contrast, chemotherapy intensification with trabectedin plus PLD increases tumor response and progression-free survival but does not establish an overall survival advantage and substantially increases severe adverse events.

The novelty of this review lies in its comparative synthesis of phase III evidence, emphasizing that chemotherapy selection in platinum-resistant ovarian cancer should not be based solely on tumor response or treatment intensity, but rather on a balance of efficacy, toxicity, and clinical feasibility. Accordingly, treatment decisions should prioritize tolerability, symptom control, and individual patient goals. Future therapeutic advances require greater emphasis on biomarker-directed and targeted approaches to overcome platinum resistance rather than further intensification of conventional cytotoxic chemotherapy.

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