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Pegylated liposomal doxorubicin combined with carboplatin: A rational treatment choice for advanced ovarian cancer

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Contents

Abstract

Objective: Many questions remain unanswered regarding the optimal treatment paradigm for ovarian cancer, and alternatives for both first- and second-line therapy are needed.
Methods: This review summarizes recent data with the combination of pegylated liposomal doxorubicin (PLD) and carboplatin in ovarian cancer.
Results: Anthracyclines are active in ovarian cancer and lack the neurotoxic effects of taxanes. PLD has reduced cardiotoxic potential vs non-liposomal doxorubicin and is the only non-platinum monotherapy to demonstrate a significant survival advantage as second-line treatment of ovarian cancer. Replacing the taxane with PLD in platinum doublets for either first-line or recurrent ovarian cancer (ROC) has been or is being evaluated in more than 1600 patients. Studies evaluating PLD plus carboplatin in platinum-sensitive ROC have shown that the regimen is tolerable and active.
Conclusion: PLD–carboplatin is a promising chemotherapy combination. Phase III trials will elucidate whether it represents a new standard of care in ovarian cancer.

Keywords: Pegylated liposomal doxorubicin; Carboplatin; Platinum; Chemotherapy; Anthracycline; Ovarian cancer; Recurrent; Advanced disease

1. Introduction

According to 2002 estimates, over 200,000 women are diagnosed with ovarian cancer worldwide, and approximately 125,000 die from this disease each year [1]. The current stan-

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dard first-line chemotherapy for advanced ovarian cancer, paclitaxel–carboplatin, represents progress toward improving outcomes. Nevertheless, fewer than half of patients achieve 5-year survival with this regimen [2,3]. Furthermore, neuropathy remains an important issue for patients on paclitaxel–carboplatin. Approximately three-fourths of all patients experience some level of neuropathy while on this regimen, and about 7% suffer from grade 3 or higher intensity [2,3]. Neurotoxicity of any grade persisting after carboplatin–paclitaxel completion has been reported in 34% of patients after 12 months and 18% after 24 months [2]. A retrospective study of residual toxicity experienced by patients who received paclitaxel–carboplatin confirmed the long-lasting pattern of recovery, demonstrating that 14% of patients suffered residual neuropathy 1 year following treatment completion [4]. Persisting neurotoxicity induced by first-line therapy may be present in a significant proportion of patients while experiencing relapse and, therefore, may affect second-line treatment choice.

Following first-line therapy, clinicians are faced with a myriad of choices with which to treat patients. The time remaining free of progression following the initial platinum regimen (platinum-free interval [PFI]) offers some guidance on which regimen to choose (platinum or non-platinum). Two randomized phase III trials have shown platinum-based combination therapy provided superior results compared with mainly single-agent platinum in platinum-sensitive relapsed disease with PFI longer than 6 months [5,6]. However, platinum sensitivity is not a biological rule following an exact time pattern. Longer PFI increased the chances for a benefit by platinum re-challenge, especially for PFI longer than 12 months [7,8]. Therefore, patients who relapse 6–12 months following the end of their initial regimen may benefit less and have been classified as partially sensitive [7–10]. The latter represents a challenging gray zone with respect to further use of platinum agents and combination partners. Thus, there is a critical need for non-neurotoxic drugs in this setting.

Anthracyclines have long been known to be active in ovarian cancer [11] and are devoid of the neurotoxic effects that plague the taxanes. Data from meta-analyses have shown a survival benefit for the addition of doxorubicin in the first-line treatment of advanced ovarian cancer in the pre-taxane era [12]. However 2 phase III trials failed to demonstrate that the addition of epirubicin to paclitaxel–carboplatin improves overall survival (OS) or progression-free survival (PFS) [13,14] in first-line ovarian cancer. Now the availability of liposomal formulations has renewed an interest in studying anthracyclines in ovarian cancer.

Use of anthracyclines in a platinum doublet has not been fully explored in the first- or second-line setting. In the first-line setting, replacing the taxane with an anthracycline may reduce the concern of introducing neurotoxicity early in therapy and may maintain patient quality of life (QOL) for a longer period of time. In the second-line setting, the ICON4 trial demonstrated that a combination of paclitaxel with platinum chemotherapy prolongs survival compared with carboplatin without taxanes in patients with platinum-sensitive recurrent ovarian cancer [5]. In addition, the combination of gemcitabine with carboplatin has shown superior response rate and PFS compared with carboplatin monotherapy in a similar setting [6]. The latter regimen showed less neurotoxicity but was associated with far higher myelosuppression than the taxane combination. Therefore, further regimens were evaluated.

Pegylated liposomal doxorubicin (PLD), a formulation of doxorubicin encapsulated in liposomes and coated with methoxypolyethylene glycol, promotes an enhancement of circulation time of drug in the blood and localization in the tumor [15]. These modifications improve the toxicity profile of doxorubicin, whereby cardiotoxicity is reduced compared to conventional doxorubicin. In a randomized trial comparing PLD with doxorubicin in metastatic breast cancer patients, the risk of developing cardiotoxicity was significantly higher for patients receiving doxorubicin than for those receiving PLD ($p < 0.001$, hazard ratio [HR] = 3.16 for comparison of cumulative anthracycline dose at the first cardiac event) [16]. The incidence of myelosuppression, vomiting, and alopecia were also decreased with PLD compared with doxorubicin; however, the incidence of mucositis/stomatitis and palmar–plantar erythrodysesthesia [PPE] were increased.

PLD is the only non-platinum single-agent to demonstrate a significant survival advantage in the second-line treatment of ovarian cancer. A phase III randomized trial compared PLD with topotecan in 481 patients with either platinum-sensitive (PFI > 6 months) or platinum-refractory (PFI ≤ 6 months) recurrent ovarian cancer [17]. Mature survival data demonstrated a significant benefit for PLD in the intent-to-treat population (HR = 1.23 [95% CI 1.01–1.50]; $p = 0.038$) which was pronounced in patients with platinum-sensitive disease (HR = 1.432 [95% CI 1.066–1.923]; $p = 0.017$).

A phase III trial (Multicentre Italian Trials in Ovarian cancer [MITO]-3) demonstrated comparable efficacy and improved QOL with PLD monotherapy compared with gemcitabine monotherapy in patients with recurrent ovarian cancer and a PFI of <12 months [18]. No difference in survival between the 2 groups was shown in the subset of patients with a PFI ≤ 6 months. However, a statistically significant improvement in survival was observed with PLD in those with PFI of 7–12 months ($p = 0.013$). Patients in the PLD arm experienced statistically significantly higher global QOL scores at the first and second post-baseline QOL assessments [18].

Recently, efforts have been made to develop platinum-based regimens that are comparable in efficacy to platinum-taxane regimens with less neurotoxicity and alopecia. Based on the previous success of anthracyclines and the altered toxicity profile of PLD, this agent has been a rational choice for further evaluation in combination with platinum agents in the treatment of ovarian cancer.