Long-Term Pegylated Liposomal Doxorubicin Use in Recurrent Ovarian Carcinoma

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Background: Ovarian carcinoma is a devastating disease because patients are diagnosed with advanced disease at presentation and five-year survival ranges from 5–20%. Salvage therapy becomes important for survival in those patients with recurrent disease. There are a variety of agents with relatively similar response rates; however, side effects may limit choice. Pegylated liposomal doxorubicin was found to be less toxic but as effective as other agents. Cardiotoxicity continues to be a concern with long-term antracycline use.

Cases: We present three cases of women diagnosed with advanced ovarian carcinoma. Each patient initially underwent optimal cytoreductive surgery, however, developed recurrent disease and were treated with pegylated liposomal doxorubicin. One patient remains disease-free following complete response. Two patients were maintained on pegylated liposomal doxorubicin with stable disease for 18 and 34 months, respectively. These cases demonstrate that pegylated liposomal doxorubicin can be used for extended periods of time without cardiotoxicity.

Conclusion: The adverse events were few with cumulative doses as high as 1,360 mg/m^2. These cases show that pegylated liposomal doxorubicin may be a promising agent in recurrent ovarian carcinoma. We recognize the limitations of our data. The results need to be confirmed in a larger group of patients.

Key words: ovarian carcinoma ■ pegylated liposomal doxorubicin ■ salvage therapy

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INTRODUCTION

Pegylated liposomal doxorubicin (Doxil®: Ortho Biotech Products LP, Bridgewater, NJ) is a unique formulation of conventional doxorubicin that avoids phagocytosis, resulting in a prolonged circulation time (t ½ ~55 hours) with retention of the drug in the liposome and selective accumulation in the tumor vascular bed following extravasation through the leaky tumor vasculature.[1]

The U.S. Food and Drug Administration approved pegylated liposomal doxorubicin in June of 1999 for the treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens.

Ovarian cancer is the fifth leading cause of cancer-related deaths among women.[2] It is estimated that 23,000 new cases of ovarian cancer will have been diagnosed in the United States in 2002 and that 13,900 women will have died of the disease.[2] Moreover, many affected women experience nonspecific gastrointestinal or abdominopelvic symptoms, so a delay in confirming the diagnosis is common.[3] As a result, most women (70–75%) have advanced-stage (III–IV) disease at the time of presentation.[4]

Studies have shown that 20% of women who are initially treated with platinum-based therapies fail to respond.[5] For those women who do respond, 55–75% will relapse within two years despite optimal cytoreductive surgery and aggressive chemotherapy.[5] Five-year survival for patients ranges from 5–20%. The initial therapy for ovarian carcinoma consists of paclitaxel and a platinum-based agent.

Pegylated liposomal doxorubicin has been proven to be effective in platinum-resistant disease; however, one main concern has been the risk of cardiotoxicity with prolonged use. We have observed three cases in which long-term pegylated liposomal doxorubicin therapy has been used with the cumulative doses received ranging from 760–1,360 mg/m^2 without any cardiac events. We present our data with approval of the Institutional Review Board to demonstrate that pegylated liposomal doxorubicin therapy can be used

long-term without cardiotoxicity. Ortho Biotech has not published data on the recommended length of time for pegylated liposomal doxorubicin use. These reports may contribute to the data.

CASE REPORTS

Case 1

The patient is a 61-year-old woman who originally presented with a large pelvic mass and a CA-125 of 232 U/ml. She underwent optimal cytoreductive surgery for a stage-IIIC papillary serous ovarian carcinoma followed by adjuvant chemotherapy. Her chemotherapy regimen consisted of induction therapy with cisplatin at 50 mg/m^2 followed by four cycles of cisplatin (50 mg/m^2), doxorubicin (50 mg/m^2) and cyclophosphamide (750 mg/m^2). The CA-125 decreased to 9 U/ml, and a second-look laparoscopy was performed that was negative. She was without any evidence of disease for 21 months, at which time she was noted to have an elevated CA-125 to 41 U/ml and soft-tissue mass on computed tomography (CT) scan. Reexploration indicated recurrent disease, and chemotherapy was restarted with paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2) for 13 courses. The repeat biopsy was negative for disease, and she again remained without disease for 11 months. Recurrent disease was diagnosed, and she was retreated with paclitaxel (175 mg/m^2) and carboplatin (AUC 5) for 14 courses. CT evaluation revealed progression of disease, and her therapy was changed to Doxil 40 mg/m^2 every four weeks without event. Her baseline MUGA scan revealed a 70% ejection fraction that decreased to 57% after 19 courses (over 18 months) of therapy for a total cumulative doxorubicin dose of 760 mg/m^2 in the pegylated liposomal formulation. Upon progression of disease, she was treated with topotecan for 14 courses. She is currently alive with disease receiving etoposide due to her request for oral therapy.

Case 2

The patient is a 57-year-old woman who presented with a 6-cm adnexal mass along with a negative CA-125. She underwent optimal cytoreductive surgery for a stage-IIIC papillary serous ovarian carcinoma followed by adjuvant chemotherapy. Her chemotherapy regimen consisted of paclitaxel (175 mg/m^2) and carboplatin (AUC 5) for six courses. She was noted to have a questionable supraclavicular lymph node on follow-up CT scan one month after completion of therapy, with no other evidence of disease. She underwent a fine-needle aspiration of the lesion followed by pathologic evaluation, which revealed metastatic disease. She was then started on pegylated liposomal doxorubicin 40 mg/m^2 every four weeks. Her baseline MUGA scan revealed an ejection fraction of 71% that decreased to 68% after 22 courses for a total cumulative doxorubicin dose of 860 mg/m^2 in the pegylated liposomal formulation over 21 months with a complete clinical response. The only complication was one episode of extravasation, which was treated uneventfully with steroids. She is currently alive with no evidence of disease without any therapy.

Case 3

The patient is a 70-year-old woman who presented with abdominal pain. She underwent a CT scan that revealed a right adnexal mass, ascites, peritoneal implants and small bilateral pleural effusion, along with a CA-125 of 1,155 U/ml. She was taken to the operating room for optimal cytoreductive surgery for a stage-IIIC papillary serous ovarian carcinoma followed by adjuvant chemotherapy. Her chemotherapy regimen consisted of paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2) for six courses, with normalization of the CA-125. She underwent a second-look laparoscopy that revealed persistent disease. Paclitaxel and carboplatin were resumed for six courses, and a third-look laparoscopy revealed persistent disease. She received 25 additional courses of paclitaxel (175 mg/m^2) and carboplatin (AUC 6). A CT was performed that revealed intraabdominal disease, and her therapy was changed first to topotecan (which she did not tolerate) and then to pegylated liposomal doxorubicin at 40 mg/m^2 every four weeks without any adverse event. Her baseline MUGA scan ejection fraction was 54% and decreased to 52% after 34 courses, for a total cumulative doxorubicin dose of 1,360 mg/m^2 in the pegylated liposomal formulation. She is currently alive with disease and being treated with gemcitabine and cisplatin.

DISCUSSION

In this case report, we present three cases of patients who were treated over long intervals with pegylated liposomal doxorubicin therapy at 40 mg/m^2 to total cumulative doses as high as 1,360 mg/m^2 without any evidence of cardiotoxicity. There was one complete response, one partial response and the last patient was maintained on pegylated liposomal doxorubicin with stable disease. In addition, there was no cardiotoxicity. For years at our institution, it was our policy to obtain an MUGA scan at the commencement of therapy, at six months and then after every other cycle. Once the data were further reviewed, our policy was changed to obtain a pretreatment MUGA scan and then repeat the scan based on patient symptomalogy. The key point here is that we were able to prolong patients' lives without decreasing their quality of life.

It has been shown that patients treated with pegylated liposomal doxorubicin had a 23% objective response with measurable disease and a 31% overall

response, including biochemical responses. This study reported that no grade-3 or -4 toxicities were seen in 52 patients treated with 20 cycles of chemotherapy. Additionally, the baseline hemoglobin and the tumor burden were both predictors for time to failure.[6]

Gordon et al. performed a randomized phase-III study comparing pegylated liposomal doxorubicin with topotecan comparing the efficacy in recurrent epithelial ovarian carcinoma.[7] One aspect of the study included a quality-of-life assessment. The European Organization for Research and Treatment of Cancer Quality of Life (QlQ-C30) questionnaire, which assesses how patients are functioning (socially, cognitively, emotionally and in their respective roles), was used. The questionnaire also assesses fatigue, pain, nausea/vomiting, dyspnea, insomnia, loss of appetite, constipation and diarrhea.[7] The patients in this study completed the survey at entry, at each cycle and four weeks after the last treatment. Overall, patients tolerated pegylated liposomal doxorubicin very well. As with our patients in this report, pegylated liposomal doxorubicin is well tolerated. Two of the three patients continued to work while receiving therapy. Pegylated liposomal doxorubicin can be used in a more convenient dosing schedule and increase patient compliance due to decrease in alopecia, nausea and vomiting.

When pegylated liposomal doxorubicin is compared to the other agents that have been used for salvage therapy for ovarian cancer, the response rates are comparable. Published response rates of 12.4, 13.9. 26.8 and 18.3 are associated with topotecan,[8] gemcitabine,[9] oral etoposide[10] and pegylated liposomal doxorubicin[7] therapy, respectively.

There are no reports in the literature that show greater lengths of treatment than those presented here. Although only three cases are presented, the study proves that pegylated liposomal doxorubicin can be given over long periods of time with very minimal toxicities. In the patients presented here, there were no episodes of congestive heart failure, although one patient experienced a >20% reduction in her ejection fraction without any symptomalogy. Swain et al. have shown that total cumulative dosage is not a risk factor for doxorubicin cardiotoxicity, but age is the important factor with those >65 years having the greatest risk.[11] Lastly, we were able to stabilize disease without compromising the patients' quality of life. These are reasons why pegylated liposomal doxorubicin may be a promising therapy for patients who have failed platinum therapy.

PRECIS

Pegylated liposomal doxorubicin therapy can be used in patients with advanced ovarian carcinoma for salvage therapy without cardiotoxicity.

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