Effectiveness of a nursing support program for patients with recurrent ovarian cancer receiving pegylated liposomal doxorubicin (Caelyx®/Doxil®)

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Abstract

Pegylated liposomal doxorubicin (PLD) has become the preferred alternative for ovarian cancer patients who have failed platinum-based therapy, but side effects, such as palmar-plantar erythrodysesthesia (PPE), may lead to sub-optimal drug exposure and treatment discontinuation. A prospective Canadian multicentre open-label study evaluated the effects of a nurse-administered education and support program on treatment adherence and tolerability in 112 women with recurrent ovarian cancer. Subjects received an average of four four-week PLD cycles, the recommended number of courses required to evaluate the efficacy from PLD. Side effects were common, but 75% of patients were able to complete > 3 cycles and 59% completed > 4 cycles of PLD chemotherapy. With proactive nursing intervention, the incidence of PLD-associated grade three-four toxicities such as PPE and mucositis was substantially decreased. Nursing intervention may allow more patients to receive chemotherapy on schedule, thus reproducing the conditions of the clinical study in which the efficacy of the drug has been established.

Ovarian cancer is a leading cause of cancer death in Canadian women with an estimated 2,271 new cases diagnosed annually and 1,457 deaths. The overall five-year relative survival rate is 45%. The median age at diagnosis is 63 years; the median age at death is 71 years (Canadian Cancer Society, 2005; National Cancer Institute, 2006).

Management includes surgery and chemotherapy with a platinum/taxane combination. However, an estimated 50% of patients with advanced disease will experience a recurrence. The choice of a second-line chemotherapy is based on the initial platinum sensitivity of the tumour. Tumours that are platinum-sensitive (response lasting > 6 months) may be rechallenged with a platinum

agent alone or in combination. The International Collaborative Ovarian Neoplasm/Arbeitsgemeinschaft Gynaekologische Onkologie (ICON-4/AGO-OVAR-2.2) trial indicated that a platinum/taxane combination could improve the one-year progression-free interval by 10% over conventional platinum chemotherapy in patients with recurrent platinum-sensitive ovarian cancer (Ozols, 2005; Parmar, Ledermann, Colombo, du Bois, Delaloye, Kristensen, et al., 2003).

Patients with platinum-resistant ovarian cancer (response < 6 months) are commonly treated with pegylated liposomal doxorubicin (PLD), topotecan, etoposide, gemcitabine or vinorelbine. PLD (Caelyx®/Doxil®) is a formulation of doxorubicin contained in liposomes and coated with polyethylene glycol (PEGylated) to increase the half-life of the drug and promote more targeted delivery to the tumour. PLD is approved for use in Canada for the treatment of advanced ovarian cancer in patients who have failed standard first-line platinum- and paclitaxel-based chemotherapy; as monotherapy for patients with metastatic breast cancer in whom there is an increased cardiac risk; and for the treatment of AIDS-related Kaposi's sarcoma patients who have failed or cannot tolerate systemic combination chemotherapy. The usual recommended dose is 50 mg/m² every four weeks, although some analyses have indicated that a dose of 40 mg/m² may have comparable efficacy and a more favourable side-effect profile. Treatment is generally administered until disease progression. While the number of planned cycles is not fixed, it is recommended that patients receive at least four cycles of PLD before efficacy is assessed (Gabizon & Martin, 1997; Rose, Maxson, Fusco, Mossbruger, & Rodriguez, 2001; Campos, Penson, Mays, Berkowitz, Fuller, Goodman, et al., 2001).

Two phase II studies of PLD in patients with platinum/paclitaxel-refractory ovarian cancer demonstrated an overall response rate of 17% to 25%. A phase III trial in platinum-resistance and sensitive women reported that PLD 50 mg/m² given as a one-hour infusion every four weeks was as effective as topotecan 1.5 mg/m² given as a 30-minute infusion for five days every three weeks. Furthermore, a long-term survival analysis showed that patients treated with PLD had a significantly longer overall median survival versus topotecan. The most significant difference observed was in the subset of patients with platinum-sensitive disease (Muggia, Hainsworth, Jeffers, Miller, Groshen, Tan, et al., 1997; Gordon, Granai, Rose, Hainsworth, Lopez, Weissman, et al., 2000; Gordon, Fleagle, Guthrie, Parkin, Gore, & Lacave, 2001; Gordon, Tonda, Sun, & Rackoff, 2004).

PLD is relatively less toxic than topotecan or conventional doxorubicin, however, side effects such as palmar-plantar erythrodysesthesia (PPE, hand-foot syndrome [HFS]) may lead to sub-optimal drug exposure and treatment discontinuation (Gordon et al., 2001; Gabizon, 2001).

Physicians and nurses are cancer patients' primary source of information about medications and side effects. As Gordon and Butler (2003) have noted, oncology nurses play a vital role in preparing patients to make treatment decisions, providing education about

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medication-related side effects, and serving as patient advocates to ensure quality of life (Nair, Hickok, Roscoe, & Morrow, 2000; Gordon & Butler, 2003).

It was hypothesized that a nursing support program, comprising patient education about potential toxicities and how to manage them, could potentially improve treatment outcomes by decreasing the occurrence and/or severity of PLD-related adverse events. All nurse participants in the program attended a training session to review the study protocol and discuss possible PLD-associated adverse events. Participants received patient education kits, which included a patient booklet on PPE, a Symptom Tracker diary, a list of hints to reduce PPE risk (Table One), and products to minimize PPE symptoms (e.g., hand cream, foot cream, cushioned insoles). The training session provided instructions on completing the case report forms that were to be submitted every two cycles.

Design

A total of 112 ovarian cancer patients who relapsed after one or more prior courses of platinum-based chemotherapy were accrued at eight Canadian centres. PLD was administered as second-, third- or

fourth-line therapy in 54%, 33% and 9% of patients, respectively. The majority of patients (85%) received a paclitaxel/platinum combination as first-line therapy. The median patient age was 62 years (range 32 to 87 years). The average dose of PLD was 40.7 mg/m² (range 35 to 50 mg/m²) every 28 days for an average of 4.01 cycles (range one to 13 cycles). PLD was administered as monotherapy in 101 patients (90.2%) while 11 patients received a combination of PLD and cisplatin or carboplatin.

Prior to PLD initiation, oncology nurses educated patients during one-on-one sessions about the chemotherapy regimen and its potential side effects. Informed consent was obtained prior to study entry. Nurses provided all patients with a booklet, **Information for Patients Receiving Caelyx**, which explained ovarian cancer, chemotherapy, potential treatment-related side effects, and how to manage or prevent PPE (Table One). Patients were instructed to contact the oncology nurse, physician or pharmacist immediately if key symptoms occurred, including skin changes on the hands and feet, dyspnea or chest pain, mouth sores, fever or other signs of infection. PPE grading was standardized according to the grading system described in Table Two (Gordon et al., 2000).

The information booklet also contained a Symptom Tracker diary, in which patients were instructed to record medications (including nonprescription and alternative remedies) on a daily basis. Blood test results, severity of side effects, mood and questions to ask the physician or nurse at the next scheduled visit were also recorded. The side effects listed in the booklet for self-monitoring included nausea, vomiting, mouth sores, skin reactions, diarrhea, fever, loss of appetite, fatigue and hair loss. Symptoms were rated from one (mild) to three (severe) in accordance with the Common Terminology Criteria for Adverse Events (NCI CTCAE version two). The nurse reviewed the diary entries at each follow-up visit, re-explained measures to prevent and/or treat side effects, and reinforced the importance of completing the diary cards and of remaining on therapy. Follow-up visits were scheduled every four weeks in conjunction with patients' infusion visits. Patients were instructed to contact the nurse or other clinic personnel between visits, if needed.

The case nurse reviewed the medical record and completed case report forms after every two cycles. All nurse investigators attended a training meeting prior to the start of the study to ensure uniformity of case reporting and chart reviews. Case report forms included information on demographics, disease and treatment history, PLD regimen and current clinical status. Case report forms were submitted for data analysis upon discontinuation of PLD therapy or after cycle six of therapy.

Table One. Information provided to patients to manage side effects

Hand-foot syndrome:

- Do not expose your skin to very hot water
- Avoid tight-fitting footwear or high-heeled shoes
- Avoid vigorous exercise that might cause trauma to your feet
- Keep your hands and feet uncovered
- Do not rub your skin vigorously
- Pat your skin dry after bathing
- Do not use abrasive washcloths
- Soak your hands and/or feet in basins of cold water whenever possible
- Stay in cool places
- Take cool baths or swim (in non-chlorinated water)

Nausea/vomiting:

- Talk to your doctor about medications to prevent or control nausea and vomiting
- Brush your teeth frequently
- Eat and drink slowly
- Keep yourself hydrated
- Eat smaller meals more often
- Rest for a bit after eating
- Nibble on dry foods
- Avoid liquids during meals
- Avoid unpleasant sights, odours or sounds
- Avoid strong odours
- Wear loose-fitting clothing
- Avoid sweet, fried, greasy and spicy foods
- Have someone cook for you

Fatigue:

- Take frequent breaks or naps
- Alternate periods of rest with periods of activity
- Participate in a planned exercise program
- Save your energy for activities that are important to you. Put other tasks aside or have someone do them for you
- Eat. Food gives your body fuel. Try to eat as nutritiously as possible
- Ask your doctor if you have anemia. If you do, medications may help you
- Try relaxation techniques such as meditation, visualization or prayer to relax and rejuvenate
- Avoid caffeine in the afternoon and evening

Table Two. Grading of palmar-plantar erythrodysesthesia (Adapted from Gordon et al., 2000).

Grade	Clinical signs	Notes
1	• Mild erythema, swelling or desquamation	Does not interfere with daily activities
2	• Erythema, swelling or desquamation; small blisters or ulcerations (< 2 cm)	Interferes but does not preclude daily activities
3	• Blistering, swelling or ulceration	Interferes with walking or other normal activities. Cannot wear regular clothing
4	• Life-threatening • Diffuse or local process causing infectious complications	Confined to bed or requires hospitalization

Results

A total of 111 of 112 patients (99.1%) received the diary at study entry. Ninety-two patients (82%) had completed the diary at the end of cycle one, 54 of 63 patients (86%) at the end of cycle four and 21 of 30 (70%) at the end of cycle six. More than 95% of patients followed the nurse's advice regarding side-effect management.

Seventy-eight patients (69.6%) reported at least one adverse event. Among patients reporting an adverse event, the mean number was 3.3 events. Common graded events included skin toxicity (50%), mucositis (38%) and decreased blood count (15%) (Figure One). Thirty-four of 112 patients (30.4%) had 62 serious adverse events (all grades three/four irrespective of causality). There were 20 deaths, primarily due to disease progression. No death was related to PLD administration. Serious adverse events (grades three/four) possibly related to PLD included fatigue (25%), nausea/vomiting (10%), skin toxicity (3.5%), mucositis (3%) and decreased blood count (2%). Skin toxicity was the most common reason for a delay/reduction (7%) in PLD or cessation of therapy (3%) (Table Three). There were 15 hospitalizations. The most common reason for hospitalization was nausea/vomiting (8%).

Figure One. Frequency of graded potentially drug-related adverse effects in PLD-treated ovarian cancer patients who failed to respond adequately to prior platinum-based chemotherapy

Hematologic toxicity was managed with hematopoietic growth factors (e.g., granulocyte-macrophage colony-stimulating factor, erythropoietin) or blood transfusion, required in five patients (4.5%). Medical and/or nursing interventions for serious adverse events included PLD dose modification and the use of udder balm (vitamins A, D and E/lanolin/aloe vera), pyridoxine/vitamin B6 or dexamethasone for PPE; use of a medicated mouthwash for mucositis; and antiemetic medications (e.g., prochlorperazine, granisetron, ondansetron, diphenhydramine) for nausea/vomiting.

Nurses reinforced patients' education and reviewed their diary entries in 87 of 92 patients who completed their diary (94.5%) at the end of cycle one, 47 of 54 patients (87.0%) at the end of cycle four, and 19 of 21 patients (90.5%) at the end of cycle six.

As recurrent ovarian cancer is a heterogeneous disease, a fixed number of cycles is not planned; treatment is generally continued until disease progression. However, it is recommended that the patient receive at least four cycles before the efficacy of the drug is assessed. A total of 51 of 112 patients (45.5%) received one to three cycles of PLD, 55 patients (49.1%) received four to eight cycles, and five patients (4.5%) received nine or more cycles. One patient (0.8%) was unable to complete one cycle of therapy. The average number of cycles received was 4.01. The median duration of treatment was 84 days.

Seven patients (6.3%) discontinued treatment due to adverse events, including cutaneous reaction (n=3), bowel obstruction (n=2), fatigue (n=1) and pleural effusion (n=1); four (3.6%) could be potentially related to PLD. There were three cases of cardiotoxicity, including one patient with signs/symptoms of congestive heart failure.

Clinical response, as determined by examination and/or radiological evaluation, was improved or stable in 70 of 107 patients (65.4%) assessed at the end of cycle two, 42 of 79 patients (54.2%) at the end of cycle four, and 25 of 37 patients (67.5%) at the end of cycle six (Table Four).

Discussion and conclusions

In this study, the frequency of adverse events associated with the use of pegylated liposomal doxorubicin (Caelyx®/Doxil®) was comparable to that previously reported in a phase III trial. However, during the nursing intervention program, the incidence of

Table Three. Impact of adverse events on PLD dosing among 112 patients with recurrent ovarian cancer

	NA		None		Delay/reduce dose		Stop therapy	
	N	%	N	%	N	%	N	%
Decreased blood count	50	44.6	58	51.8	4	3.6	0	0.0
Skin toxicity	34	30.4	67	59.8	8	7.1	3	2.7
Mucositis	39	34.8	72	64.3	1	0.9	0	0.0
Fatigue	19	17.0	87	77.7	1	0.9	5	4.5
Nausea/Vomiting	28	25.0	77	68.8	3	2.7	4	3.6

grades three/four toxicity was substantially reduced. In the study by Gordon et al., 117 of 239 patients (49%) developed PPE (all grades) using the same toxicity criteria, including 55 cases (22.8%) that were grades three/four. In the present study, 59 of 112 patients (52.7%) reported PPE, of which four cases (3.5%) were grades three/four. Similarly, the incidence of grades three/four mucositis was decreased from 8.3% in the phase III study to 3% in the present study (Gordon et al., 2001).

The improvement in side-effect management seen with the nursing intervention program was associated with somewhat fewer discontinuations. In the study by Gordon et al. (2001), PPE was the most common adverse event and was managed primarily by dose reduction or delay; nine patients (3.8%) required discontinuation of therapy. In the present study of heavily pretreated subjects, three patients (3%) discontinued PLD treatment due to severe PPE. No discontinuations occurred in the subgroup of patients receiving PLD in combination with platinum-based therapy.

While this study indicates that patient education can reduce the severity of treatment-limiting side effects, it has some limitations compared to a standard clinical study. The study population was heterogeneous and included patients receiving second-, third-, and fourth-line therapy. Thus, these patients may have had more advanced disease than those enrolled in the Gordon et al. (2001) study. Further, patients have a highly variable response to chemotherapies and some side effects may be observed despite optimal nursing intervention.

The present nursing intervention program, comprising patient education about potential side effects and the importance of effective prevention and management, may have helped to reduce the severity of PPE and mucositis in patients receiving PLD. The improved tolerability seen with targeted side-effect management could enable clinicians to optimize the duration of PLD chemotherapy and enhance quality of life for women with recurrent epithelial ovarian cancer.

Table Four. Clinical response according to duration of therapy in 107 patients with recurrent ovarian cancer treated with PLD who completed two or more cycles

At the end of	Improved		Stable		Progression	
	N	%	N	%	N	%
Cycle 2 (n = 107)	10	9.3%	60	56.1%	37	34.6%
Cycle 4 (n = 79)	15	19.0%	27	34.2%	37	46.8%
Cycle 6 (n = 37)	10	27.0%	15	40.5%	12	32.4%
Cycle 8 (n = 13)	2	15.4%	6	46.2%	5	38.5%
Cycle 10 (n = 5)	2	40.0%	1	20.0%	2	40.0%

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