Women diagnosed with stage III or IV ovarian cancer typically are treated with surgery followed by chemotherapy. Intraperitoneal (IP) chemotherapy, the direct administration of chemotherapy into the IP cavity, has been explored as a viable treatment option for some women with advanced ovarian cancer. Fatigue may occur as a result of the disease process, treatment, or a wide variety of physical, psychological, or situational factors. Fatigue is one of the most common and distressing side effects associated with chemotherapy and it may be intensified in women receiving IP chemotherapy. The purpose of this article is to examine fatigue in women receiving IP chemotherapy for advanced ovarian cancer and to examine what aspects of IP chemotherapy may contribute to fatigue development. Factors reviewed include surgery for debulking the tumor and placement of the IP catheter, administration of IV chemotherapy in addition to IP chemotherapy, pain, anemia, sleep disturbances, gastrointestinal disturbances, and emotional distress. Oncology nurses who are knowledgeable about the factors that contribute to fatigue in women receiving IP chemotherapy will be better prepared to conduct a comprehensive assessment and develop effective treatment strategies.
Fatigue associated with intraperitoneal (IP) chemotherapy may negatively impact the woman’s ability to function independently and her ability to withstand the rigors of IP treatment.

Cancer-Related Fatigue

Fatigue is one of the most common and distressing symptoms of cancer and cancer treatment (Curt et al., 2000; Mock et al., 2000a; Nail, 2002; Portenoy et al., 1994). More than 75% of patients with cancer receiving chemotherapy experience fatigue (Blesch et al., 1991; Irvine, Vincent, Bubela, Thompson, & Graydon, 1991; Jacobsen et al., 1999; Longman, Braden, & Mishel, 1997; Vogelzang et al., 1997), often occurring as a result of the disease process, treatment, or a wide variety of physical, psychological, or situational factors. Fatigue has been defined in numerous ways, including a lack of energy, tiredness, malaise, insomnolence, exhaustion, inability to concentrate, and lack of motivation (Aistars, 1987; Glaus, 1998; Holley, 2000; Portenoy & Itri, 1999; Winningham et al., 1994). The National Comprehensive Cancer Network (NCCN, 2007) defines cancer-related fatigue as a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer treatment that is not proportional to recent activity and interferes with usual functioning. Fatigue’s intensity may be elevated for patients receiving multimodal or dose-dense therapy, as the women receiving IP chemotherapy for ovarian cancer were. In a telephone interview conducted by Curt et al., patients with cancer reported that their fatigue was worse than their pain and that fatigue interfered with their daily lives more than nausea, pain, or depression. Increased fatigue intensity has been correlated with decreased performance status, emotional issues, muscle weakness, pain, numbness, difficulty sleeping, trouble concentrating, and heartburn (Jacobsen et al., 1999). Furthermore, it has been suggested that fatigue intensity increases as treatment protocols become more intense (Sura, Murphy, & Gonzales, 2006).

Fatigue Research

Fatigue in women with advanced ovarian cancer receiving IP chemotherapy has received little attention in the research literature. A review was conducted to determine the extent of fatigue assessment, occurrence, and prevalence in women receiving IP chemotherapy for ovarian cancer. Key words used to conduct the search included intraperitoneal chemotherapy, ovarian cancer, and clinical trials. In addition, the Cochrane Database of Systemic Reviews was explored for IP chemotherapy use in the initial management of primary epithelial ovarian cancer. Studies were reviewed to determine whether fatigue was identified as a side effect from IP chemotherapy and, if so, how fatigue was measured and what the findings were from the trial. Few studies have reported fatigue as a significant side effect of IP chemotherapy, which is surprising given that multiple studies have documented the occurrence of fatigue following treatment with chemotherapy for ovarian cancer (Herben et al., 1999; Holzner et al., 2002; Holzner et al., 2003; Payne, 2002; Terauchi et al., 2003) (see Table 1). Payne examined the trajectory of fatigue in 17 adult patients with breast and ovarian cancer and found that fatigue levels were variable over time, intensifying at three months and continuing following treatment completion. Holzner et al. (2003) examined fatigue in 98 survivors of ovarian cancer who had completed treatment at least six months previously and found that 37% continued to report issues with fatigue and a reduced quality of life. Difficulties associated with fatigue may be intensified in women receiving IP chemotherapy for advanced ovarian cancer given the additional issues associated with IP chemotherapy, such as abdominal pain and catheter-related infection. Understanding the prevalence of fatigue in women with advanced ovarian cancer is needed to develop effective interventions to alleviate or mitigate fatigue-related suffering.

Fatigue Screening

A comprehensive assessment of fatigue is vital for developing management strategies. Although numerous fatigue assessment instruments have been described in the literature, most have been designed for research purposes and not for implementation in clinical practice. In response to this concern, as well as others, NCCN developed guidelines for fatigue screening that can be quickly implemented in clinical practice to identify patients experiencing fatigue (Mock et al., 2000b). The fatigue screening guidelines employ a 0–10 scale, similar to that used for the assessment of pain in the clinical setting. A rating of 0 denotes no fatigue; 1–3 denotes mild fatigue; 4–6
denotes moderate fatigue; and 7–10 denotes severe fatigue. Further fatigue evaluation and treatment is recommended based on patients’ self-reported ratings.

In women with advanced ovarian cancer, multiple factors unique to advanced ovarian cancer and IP chemotherapy may contribute to fatigue development, including surgery for debulking the tumor and placement of the IP catheter, administration of IV chemotherapy in addition to IP chemotherapy, pain, anemia, sleep disturbances, gastrointestinal disturbances, emotional distress, and reduced physical activity.

### Factors Contributing to Fatigue

#### Surgery

Surgery is predominantly used to diagnose and treat ovarian cancer. For patients able to undergo surgery, a full staging lapa-

#### Table 1. Fatigue Findings From Clinical Trials Involving Intraperitoneal (IP) Chemotherapy

<table>
<thead>
<tr>
<th>STUDY</th>
<th>IP CHEMOTHERAPY</th>
<th>STUDY DESIGN</th>
<th>SAMPLE</th>
<th>FATIGUE ASSESSMENT</th>
<th>FATIGUE MEASUREMENT</th>
<th>RESULTS OF FATIGUE FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong et al., 2006</td>
<td>Cisplatin (IV) and paclitaxel (IV) versus paclitaxel (IV) and cisplatin (IP)</td>
<td>Phase III randomized clinical trial</td>
<td>415 patients with stage III ovarian or primary peritoneal cancer</td>
<td>Yes</td>
<td>Method of measurement not reported (assumed National Cancer Institute-Common Toxicity Criteria (NCI-CTC))</td>
<td>IV greater than grade 3 or 4 = 4% of 210 (p = 0.001) IP chemotherapy greater than grade 3 or 4 = 18% of 201 (p = 0.001)</td>
</tr>
<tr>
<td>Bos et al., 2005</td>
<td>Topotecan (IP) and carboplatin or paclitaxel (IV)</td>
<td>Phase I clinical trial</td>
<td>21 patients with stage IIb–IV cancer</td>
<td>Yes</td>
<td>NCI-CTC (version 2.0)</td>
<td>Fatigue grade 3</td>
</tr>
<tr>
<td>Francis et al., 1995</td>
<td>Paclitaxel (IP) weekly</td>
<td>Phase I clinical trial</td>
<td>33 patients with residual disease</td>
<td>Yes</td>
<td>Not reported in text</td>
<td>Highest toxicity grade for each patient</td>
</tr>
<tr>
<td>Markman et al., 2001</td>
<td>Cisplatin (IV) and paclitaxel (IV) versus carboplatin (IV) followed by paclitaxel (IV) and cisplatin (IP)</td>
<td>Phase III clinical trial</td>
<td>523 patients with stage III disease with small volume disease</td>
<td>Yes</td>
<td>None specified</td>
<td>IV grade 3 and 4 = 1% IP grade 3 and 4 = 3%–4%</td>
</tr>
<tr>
<td>Rothenberg et al., 2003</td>
<td>Paclitaxel (IV) days 1 and 2, cisplatin (IP) day 2, cisplatin (IP) day 8</td>
<td>Phase II clinical trial, comparative study</td>
<td>68 patients with stage III, optimally debulked</td>
<td>Yes</td>
<td>Method of measurement not reported (Assumed NCI-CTC)</td>
<td>Combined, toxicity grade 3 or 4 = 24%</td>
</tr>
<tr>
<td>van Rijswijk et al., 1997</td>
<td>Etoposide (IP) and cisplatin (IP) with thiosulfate (IV)</td>
<td>Clinical trial</td>
<td>29 patients with pathologically complete response or persistent disease</td>
<td>Reported malaise, no fatigue</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

rotomy is conducted to accurately stage the extent of the disease and the primary ovarian cancer is resected, typically involving a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, sampling of peritoneal fluid, peritoneal washings for cytology analysis, random biopsies of the pelvic and abdominal peritoneum, and pelvic and para-aortic lymph node sampling (Trope & Kaern, 2006). The goal of cytoreductive surgery is to lessen the tumor burden and provide the patient with a greater possibility of complete treatment response. Although definitions of optimal cytoreduction are still in review, a residual tumor less than 1 cm in diameter generally is considered optimally debulked, and suboptimally debulked disease consists of a residual tumor greater than 1–2 cm in diameter (Trope & Kaern). The distinction between optimally and suboptimally debulked is important because women who have been optimally debulked have better survival rates than those who have not (Bristow, Montz, Lagasse, Leuchter, & Karlan, 1999).
Women treated with surgery to stage and resect advanced ovarian cancer may develop fatigue for a number of reasons. The postoperative course typically includes the standard post-operative challenges of pain, nausea, vomiting, and decreased physical activity, all of which contribute to fatigue. In addition, pre- and perimenopausal women treated with cytoreductive surgery will experience menopausal symptoms, including hot flashes and night sweats, following the surgery. Women with breast cancer experiencing fatigue were bothered more by menopausal symptoms than those who were not fatigued (Bower et al., 2000). No studies were found during the literature search that examined menopause, fatigue, and ovarian cancer, therefore, the association between fatigue and menopausal symptoms in women undergoing cytoreductive surgery followed by IP chemotherapy has not been established.

Surgical placement of an abdominal port-a-cath is required for IP chemotherapy. Complications from catheters also may contribute to fatigue development or intensification. Women who develop catheter infections may experience fevers, abdominal discomfort, and decreased physical activity, which may further intensify the fatigue experience. Several studies have documented catheter complications, such as infection, pain, and bowel perforations, as well as catheter function issues such as leakage, blockage, and access difficulties with IP chemotherapy administration (Armstrong et al., 2006; Pfeifle, Howell, Markman, & Lucas, 1984; Walker et al., 2006; Yen et al., 2001).

### Chemotherapy

Fatigue is one of the most frequently reported side effects of chemotherapy (Blesch et al., 1991; Hacker et al., 2006; Hacker & Ferrans, 2003; Jacobsen et al., 1999). Women with advanced ovarian cancer generally receive combination IV chemotherapy, typically platinum- and taxane-based. Women who have undergone optimal cytoreductive surgery may receive IP and IV chemotherapy (see Table 2). The history of ovarian cancer treatment with chemotherapy agents is listed in Table 2. Both single-agent therapy and combination chemotherapy have been associated with increased fatigue levels (Escobar et al., 2004; Hussain et al., 2003; Markman et al., 2003). Several researchers have studied fatigue in women receiving chemotherapy for gynecologic cancer (Armstrong et al., 2006; Donovan & Ward,

**Table 2. Summary of First-line IV Chemotherapy Randomized Clinical Trials for Advanced Ovarian Cancer**

<table>
<thead>
<tr>
<th>CHEMOTHERAPEUTIC AGENTS</th>
<th>STUDY</th>
<th>PROTOCOL</th>
<th>NOTED TREATMENT IMPROVEMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Young et al., 1978; Kane et al., 1979</td>
<td>Cyclophosphamide, hexamethylmelamine, adriamycin, and cis-dichlorodiammine-platinum (II) combination</td>
<td>Reported increased median survival Median duration of partial response of 4 months Median duration of complete response of 9 months</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Omura et al., 1986</td>
<td>Cyclophosphamide and doxorubicin once every three weeks versus cyclophosphamide, doxorubicin and cisplatin once every three weeks</td>
<td>Cisplatin used in combination chemotherapy results in improved survival Improved overall survival to 27.8 months with cisplatin</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Omura et al., 1989</td>
<td>Cyclophosphamide and cisplatin once every three weeks versus cyclophosphamide, doxorubicin, and cisplatin once every three weeks</td>
<td>No survival advantage in first-line treatment with doxorubicin Cyclophosphamide and cisplatin becomes the preferred first-line treatment</td>
</tr>
<tr>
<td>Carboplatin introduction</td>
<td>Alberts et al., 1992</td>
<td>Cyclophosphamide and cisplatin (one every three weeks) versus cyclophosphamide and carboplatin (one every four weeks)</td>
<td>No difference in median survival in cisplatin versus carboplatin Carboplatin become agent of choice because of reduced side effects seen with cisplatin</td>
</tr>
<tr>
<td>Paclitaxel (IV)</td>
<td>McGuire et al., 1996</td>
<td>Cyclophosphamide (IV) and cisplatin (once every three weeks) (IV) versus paclitaxel (IV) (administered over 24 hours) and cisplatin (IV) (once every three weeks)</td>
<td>Increased overall median survival with paclitaxel of 38 months</td>
</tr>
<tr>
<td>Carboplatin (IV) with paclitaxel</td>
<td>Ozols et al., 2003</td>
<td>Cisplatin (IV) and paclitaxel (IV) 24 hours infusion (once every three weeks) versus carboplatin (IV) and paclitaxel (IV) administered over three hours</td>
<td>Paclitaxel (IV) with improved three hour administration time Median overall survival improved to 57.4% with paclitaxel and carboplatin</td>
</tr>
<tr>
<td>Docetaxel introduction (IV)</td>
<td>Vasey et al., 2004</td>
<td>Paclitaxel (IV) and carboplatin (IV) versus docetaxel (IV) and carboplatin (IV) (Area under the curve = 5)</td>
<td>19% reduction in the neurotoxicity seen with docetaxel Comparable clinical response in both arms Hematological toxicity of grade 3 or 4, statistically significant for neutropenia</td>
</tr>
</tbody>
</table>
Fatigue is a main symptom of anemia. The overall incidence of all grades of anemia (Hg < 11 g/dl) among common first-line chemotherapeutic agents used in advanced ovarian cancer is high. Of the platinum-based chemotherapeutic agents, cisplatin has the lowest overall incidence at 25%–30%, whereas carboplatin is as high as 90% (American Pharmaceutical Partners, 2002; Bristol-Myers Squibb, 2003). Of the taxanes, docetaxel demonstrates a higher overall incidence of anemia (90.4% versus 78% with paclitaxel) (Bristol-Myers Squibb, 2003; sanofi-aventis, 2006). The proposed future choice of paraplatin replacing cisplatin as the IP or IV chemotherapeutic agent used in randomized clinical trials on patients with advanced ovarian cancer may place patients at an even greater risk for anemia and fatigue. Most clinical trials in advanced ovarian cancer have assessed for anemia, but failed to correlate the results to fatigue levels.

### Anemia

Anemia resulting from disease and chemotherapy treatment is one of the most explored causes of cancer-related fatigue. Fatigue is a main symptom of anemia. The association between sleep disturbances and fatigue has been well-documented, and patients with cancer that experience sleep disturbances also may complain of fatigue (Berger & Higginbotham, 2000; Bower et al., 2000; Given, Given, Azzouz, & Stommel, 2001; Hacker & Ferrans, 2003; Lee, 2001). It is not clear, however, whether fatigue or sleep/wake disturbances occur first. Studies examining sleep disturbances in women with advanced ovarian cancer receiving IP chemotherapy could not be found, further reinforcing the need for study. Situational factors, such as abdominal distention following IP chemotherapy administration or abdominal pain, may lead to sleep disturbances and contribute to fatigue development or intensification. Nonetheless, patients with cancer experiencing fatigue also should be assessed for sleep disturbances in accordance with NCCN (2007) guidelines.

### Sleep Disturbance

Patients with cancer may exhibit a number of sleep disorders, such as primary insomnia, primary hypersomnia, or narcolepsy. The association between sleep disturbances and fatigue has been well-documented, and patients with cancer that experience sleep disturbances also may complain of fatigue (Berger & Higginbotham, 2000; Bower et al., 2000; Given, Given, Azzouz, & Stommel, 2001; Hacker & Ferrans, 2003; Lee, 2001). It is not clear, however, whether fatigue or sleep/wake disturbances occur first. Studies examining sleep disturbances in women with advanced ovarian cancer receiving IP chemotherapy could not be found, further reinforcing the need for study. Situational factors, such as abdominal distention following IP chemotherapy administration or abdominal pain, may lead to sleep disturbances and contribute to fatigue development or intensification. Nonetheless, patients with cancer experiencing fatigue also should be assessed for sleep disturbances in accordance with NCCN (2007) guidelines.

### Gastrointestinal Disturbances

Women with advanced ovarian cancer may be at risk for a number of gastrointestinal disturbances following IP chemotherapy administration, including nausea, vomiting, constipation, diarrhea, lack of appetite, dehydration, abdominal distention, and abdominal discomfort, all of which may contribute to fatigue. In a phase II study of combined IP and IV chemotherapy, Rothenberg et al. (2003) found that 50% of the women experienced nausea and 34% experienced vomiting. In the GOG study, women in the combined IP and IV chemotherapy arm of the study experienced significantly more gastrointestinal toxicities (24% in IV group versus 46% in IP group), which the investigators attributed to the higher doses of IV cisplatin (Armstrong et al., 2006). Although specific gastrointestinal toxicities were not described in the GOG study, they frequently include nausea and vomiting, which can lead to dehydration and lack of appetite. Nausea and vomiting, dehydration, electrolyte imbalances, and abdominal distension have been clinically observed in women...
receiving IP chemotherapy, and those receiving this treatment may not be able to keep up with the recommended oral fluid replacement or the recommended oral intake of nutrients if they are experiencing significant nausea and vomiting. In addition, abdominal distention and discomfort associated with IP chemotherapy may lead to reduced physical activity. In other patients with cancer, reduced physical activity is associated with fatigue, although this has not been documented in patients with ovarian cancer (Berger, 1998; Berger & Higginbotham, 2000; Hacker et al., 2006). All of these common gastrointestinal issues found during and following the administration of IP chemotherapy may contribute to fatigue development or further intensify the fatigue experience.

**Emotional Distress**

Impairments in emotional functioning have clearly been linked to fatigue in multiple cancer groups (Kornblith et al., 1995; Portenoy et al., 1994). Receiving an ovarian cancer diagnosis has the potential to disrupt a woman’s emotional equilibrium (Norton et al., 2005), and researchers have demonstrated that women diagnosed with ovarian cancer experience moderate to severe levels of anxiety in response to their diagnosis and treatment (Kornblith et al.; Portenoy et al.). The risk for psychological distress increases for these women because the disease usually presents in advanced stages, meaning there is a higher risk for recurrence and a poor prognosis. Patients understand early in their primary treatment that, although they may obtain an initial response to treatment, disease recurrence is probable. As a result, women with ovarian cancer may experience emotional distress associated with the fear of recurrence (Bodurka-Bevers et al., 2000; Ersek, Ferrell, Dow, & Melancon, 1997).

The relationship between emotional and physical function also has been examined in several studies of women with ovarian cancer (Bodurka-Bevers et al., 2000; Kornblith et al., 1995; Portenoy et al., 1994). Decreased physical function in women with ovarian cancer has been associated with increased psychological distress, such as anxiety and depression (Kornblith et al.). In addition, receiving IP chemotherapy to treat ovarian cancer has the potential to evoke anxiety in many women, possibly from the complicated logistics of IP chemotherapy administration and the time required for drug absorption. Patients’ concerns about the ability to care for self or family responsibilities may cause further anxiety and intensify the fatigue experience. Depression, another aspect of emotional distress, also has been linked to fatigue (Fox & Lyon, 2007). Depression was the strongest predictor of fatigue in women with breast cancer (Bower et al., 2000). Fatigued women scored more than twice as high on the depression scales than those who did not show signs of fatigue.

**Nursing Implications**

Women receiving IP chemotherapy for advanced ovarian cancer may be at increased risk for developing fatigue. Few studies in the literature review examined fatigue in women receiving IP chemotherapy, but those that did found statistically significant levels of fatigue, an important finding for oncology nurses as the NCI clinical announcement prompted increased use of IP chemotherapy for first-line treatment of advanced ovarian cancer (NCI, 2006b). The challenge for oncology nurses is balancing the understanding of the potential long-term benefits of this recommended treatment with potential increased fatigue levels. Despite few studies investigating or reporting fatigue as a significant side effect of IP chemotherapy, increased levels of fatigue are observed in the clinical arena. Awareness of potential increased fatigue levels is imperative to patients, their families, and healthcare providers if successful QOL and clinical outcomes are to be obtained.

Oncology nurses play an integral role in fatigue screening and assessment, as well as the management and evaluation of interventions to manage fatigue. The NCCN guidelines for fatigue management suggest that the patient and family be counseled about the expected fatigue levels associated with a particular treatment prior to the start of that treatment. In women receiving IP chemotherapy, counseling should include information regarding the surgery, chemotherapy, and practical strategies to facilitate administration of IP chemotherapy and the subsequent fluid absorption. In addition, women and their families should receive information related to the side effects of chemotherapy, such as nausea and vomiting and fluid and electrolyte imbalances, which may contribute to fatigue development. IP chemotherapy administration is a complex process and patients will require frequent assessments of fatigue and the potential contributing factors that may influence the fatigue experience. Unfortunately, little information is available about the prevalence or severity of fatigue in women receiving IP chemotherapy. The Oncology Nursing Society’s (2005) Putting Evidence Into Practice® (PEP) card details fatigue management strategies based on research evidence (see Table 3).

**Implications for Future Research**

The literature review suggests the need for further research into fatigue prevalence and severity in women receiving IP chemotherapy for advanced ovarian cancer as well as effective management strategies for preventing and/or treating cancer-related fatigue. In this population, burden placed on the patient may be a cause for concern because of the seriousness of the advanced disease and complexity of administering IP chemotherapy. In the GOG study, only 42% of the women in the IP chemotherapy arm completed the planned six cycles of IP chemotherapy. Data collection, such as brief fatigue assessments and real-time data collection strategies, may help reduce the burden and enhance treatment adherence. These strategies have been successfully used with other patients with cancer receiving intensive therapy when patient burden was a primary concern (Hacker & Ferrans, 2006).

Symptom clustering in women receiving IP chemotherapy is another area requiring further research. Fatigue, depression, and pain have been strongly associated in other cancer populations (Miasowski et al. 2006). Although these symptoms do occur in patients with advanced ovarian cancer, it is not known whether they would cluster together in women receiving IP chemotherapy.
Fatigue management also requires further research. At the present time, exercise is the only effective strategy for reducing fatigue; however, no studies were found that tested exercise interventions in women receiving IP chemotherapy. One challenge with implementing a structured exercise intervention may be related to the feasibility of adhering to an exercise intervention during a complex treatment protocol.

Conclusion

Advanced ovarian cancer has not received the attention of other cancers in literature focusing on fatigue. One in 71 women will develop ovarian cancer during their lifetime (National Cancer Institute, 2006a). Epithelial ovarian cancer comprises 90% of ovarian malignancies, with an incidence rate of 57 per 100,000 women (NCCN, 2007), and 70% will present with advanced disease (NCCN). Women with advanced ovarian cancer may experience fatigue as a result of their disease process, treatment, or a number of other physical, psychological, or situational factors. IP chemotherapy administration may intensify fatigue that women with advanced ovarian cancer experience.

A primary role of oncology nurses is to develop successful screening and assessment strategies to identify fatigue in women with advanced ovarian cancer receiving IP chemotherapy. Because this is a unique population, strategies to effectively assess all potential contributing factors should be developed and be appropriate for implementation in the clinical arena. With this information, effective approaches for managing fatigue can be implemented to mitigate the impact of fatigue on QOL outcomes.

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References


