

Quality of Life in Patients Receiving Treatment for Gynecologic Malignancies: Special considerations for patient care

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ABSTRACT

Advances in the treatment of gynecologic cancer have extended the duration of survival of many patients. However, these patients frequently experience a variety of treatment- and disease-related side effects that diminish their quality of life (QOL) during and after treatment; among these are pain, nausea and vomiting, anemia, fatigue, peripheral neuropathy, emotional distress, and sexual dysfunction. Given the gains in survival time, patient care is being expanded to include enhancement or preservation of QOL in addition to early diagnosis and disease treatment, thus treating the whole person. In parallel with this evolution in cancer care, supportive measures are being increasingly recognized as crucial to effective patient management. This paper reviews some of the potential causes of diminished QOL in gynecologic cancer patients and basic treatment strategies for their control, with a focus on short-term QOL issues. It is important that clinicians monitor QOL during the course of the disease and its treatment, utilize procedures and therapeutic agents that take patient preferences and QOL into account, and proactively prevent and treat relevant symptoms.

Key-words: quality of life, gynecologic malignancies, cervical, endometrial, ovarian, pain, sexual function, anemia, epoetin alfa

INTRODUCTION

Advances in the early detection and treatment of gynecologic malignancies have provided gains in patient survival time (Armstrong 2002). However, these gains are often accompanied by a variety of treatment-associated toxicities that diminish the patient's quality of life (QOL) during and after treatment. Standard cancer treatments, including surgery, chemotherapy, and radiation therapy, have all been implicated in the induction of QOL-diminishing toxicities. Additionally, the patient may experience disease-related symptoms that adversely affect QOL.

In contrast to earlier goals of therapy that focused on tumor response and survival, management of cancer patients has expanded to include treatments that address not only the quantity of life, but also its quality. Given this changing paradigm, supportive care is being increasingly recognized as a key component in routine cancer management. Numerous highly effective treatments are now available to help manage many of the treatment-associated toxicities and disease-associated symptoms that diminish patients' QOL, including antiemetics, analgesic options, erythropoietic stimulating agents (recombinant human erythropoietin), psychostimulants, and antidepressants, as well as behavioral counseling strategies. This review focuses on a number of treatment-related toxicities and conditions that commonly cause impairments in QOL in patients with gynecologic cancer, and on pharmacologic and nonpharmacologic approaches

for dealing with short-term QOL issues in patients with these diseases.

ASSESSING QUALITY OF LIFE

Assessing QOL status in cancer patients is important for several reasons, particularly because it provides supplementary information about the impact of the disease and its treatment on cancer patients to aid physicians in selecting both antineoplastic and supportive-care therapy. Given the chronic and often incurable nature of many gynecologic malignancies, the toxicity and tolerability of a specific therapy can be as important as its efficacy, as is the ability to help ameliorate or prevent many of the associated toxicities that negatively affect QOL.

Several excellent instruments are available to measure health-related QOL in patients with gynecologic cancer. A typical approach combines a generic health status assessment such as the European Organization for Research and Treatment of Cancer QLQ-C30 (Aaronson 1993), or the Functional Assessment of Cancer Therapy-General (FACT-G), with a more targeted set of questions specific to a given tumor type. Basen-Engquist et al. validated a set of questions targeted to ovarian cancer which, when added to the FACT-G, is referred to as the FACT-Ovarian (FACT-O) (Basen-Engquist 2001). The core questionnaire (FACT-G) primarily evaluates the patient's physical, social/family, emotional, and functional well-being. The 13-item, ovarian cancer-specific subscale

assesses severity of problems that can be addressed through proper disease management (Cella 1993; Fish 1999; Basen-Engquist 2001). The FACT-O can be used alone or in combination with other scales and subscales of the FACT, such as the FACT/GOG-Ntx subscale (Calhoun et al. in press; Cella et al. 2003b), if neurotoxicity is of concern, or the Anemia subscale or Fatigue subscale if one is interested in these specific issues. Each of these scales provides QOL information relevant to a specific condition (such as fatigue) for which intervention could be useful, thus potentially improving total patient care.

COMMON SYMPTOMS ASSOCIATED WITH GYNECOLOGIC CANCERS: TYPE AND MANAGEMENT

Managing QOL in gynecologic cancer patients requires careful consideration of a variety of issues, many of which revolve around the surgical procedures employed and major side effects induced by the therapeutic agents used, as well as disease-associated factors that can negatively affect QOL. Prominent among the toxicities and symptoms that can diminish QOL in gynecologic cancer patients are pain, emotional distress, neuropathy, alopecia, nausea and vomiting, anemia, and fatigue (Steginga 1997; Harper 2000; Khayat 2000; Wilmoth 2000; Pignata 2001; Brassil 2002; Tabano 2002). Several of the major toxicities and symptoms and their management are discussed in the sections that follow, and some basic treatment strategies for managing surgery- and chemotherapy-related factors that impair QOL are summarized in Table 1.

Pain

Cancer patients frequently experience pain as a result of their disease or treatment strategies such as surgery. This symptom is considered by many clinicians and researchers to be one of the most important factors affecting the patients' QOL (Rummans 1998). Results of a survey of ovarian cancer patients undergoing chemotherapy or surgery at a cancer center indicated that 62% of the patients ($n=151$) had experienced pain prior to onset or recurrence of their disease, and 42% had experienced persistent or frequent pain within the 2 weeks prior to their participation in the survey (Portenoy 1994). Another study found that 47% of women ($n=97$) reported experiencing pain after breast cancer surgery (Miaskowski 1995). In these

studies, pain was variously shown to adversely affect cancer patients' mood, activity, work, enjoyment of life, and overall QOL. In a relevant study in patients with recurrent breast ($n=64$) or gynecologic cancer (ovarian, endometrial/uterine, cervical, other; $n=53$), pain frequency, amount, and interference with activity were found to be strongly associated with physical and social functioning, leading the authors to suggest that intervention to preserve these domains by controlling pain may have a positive impact on QOL (Rummans 1998). Fortunately, pain in cancer patients is nearly always controllable; however, it is often undertreated due to clinicians' lack of knowledge regarding pain assessment and management, patients' resistance to pain treatment due to fear of addiction to narcotic analgesics, underreporting of pain, or noncompliance with analgesic therapy (Portenoy 1999a; Harper 2000, Walsh 2000).

Treatment

Pain in gynecologic cancer patients is most often associated with late stage/recurrent disease and is typically chronic; however, it may also be related to cancer surgery, and thus can be acute in nature. Management of both acute and chronic pain in gynecologic cancer patients is based on nonopioid and opioid analgesia. The World Health Organization (WHO) has developed a three-step "analgesic ladder" to serve as a guide for analgesic therapy (Fig. 1) (WHO 1990). The basic concept is to escalate analgesic therapy from a nonopioid (eg, acetaminophen, nonsteroidal anti-inflammatory) to a weak opioid, and then to a stronger opioid, depending on pain severity and response (Levy 1996; Walsh 2000). Adjuvant drugs may be added at the various steps as indicated (eg, a tricyclic for underlying depression or insomnia). In cases where moderate to severe pain is anticipated to last 48–72 hours, or there are concerns about compliance, drug diversion, or drug abuse, transdermal fentanyl may be useful. Importantly, the selected analgesic(s) must be administered at dosages adequate to maintain a continuous level of pain control and help prevent its recurrence (Tabano 2002).

A number of nonpharmacologic therapies taught by healthcare providers, such as imagery, distraction, and therapeutic use of music, are occasionally helpful in managing pain, as are some "home remedies", including the use of hot/cold packs, massage, and mentholated topicals. A study of pain management strategies used by ambulatory breast and gynecologic cancer patients with postoperative pain found that relaxation strategies (breathing, imagery, music, meditation) are being used more frequently than in the past (Kwekkeboom 2001).

Table 1
Treatment strategies for surgery- and chemotherapy-related factors that impair QOL

Factor	Treatment Strategy
Pain ^a	<ul style="list-style-type: none"> • For mild to moderate pain, administer aspirin, acetaminophen or nonsteroidal anti-inflammatories • Maximize nonopioid dosage and add low-potency opioid (eg, codeine, oxycodone, hydrocodone) if pain increases or is persistent • For moderate to severe pain unresponsive to a maximal-dose low-potency opioid, administer high-potency opioids (eg, morphine, oxycodone, hydromorphone, fentanyl) • Administer adjuvant therapy as indicated (eg, nonsteroidal anti-inflammatory, corticosteroid, tricyclic antidepressant) • Treat any analgesic-related side effects (eg, constipation, nausea/vomiting, unclear thinking) without delay • General: Heat or cold application, counterstimulation (transcutaneous electrical nerve stimulation), distraction/reframing, hypnosis, counseling, occupational therapy aids, physical therapy appliances
Emotional distress ^b	<ul style="list-style-type: none"> • Establish a supportive, empathic, nonjudgmental relationship with patient • Allow time for the patient to communicate her concerns • Consider brief counseling; relaxation tapes for anxious patients • Consider appropriate drug therapy (antidepressants, anxiolytics), with selection based on efficacy as well as drug interaction and QOL impact
Surgery ^c	<ul style="list-style-type: none"> • Minimize blood loss (transfusion or rHuEPO as appropriate) • Treat cancer with cytoreductive surgery, chemotherapy, or radiation therapy (or a combination of these) as appropriate. Consider interval debulking surgery; however, definitive information on QOL aspects of this procedure is very limited • Where appropriate, consider using conservative surgical approaches (eg, sentinel node procedure, trachelectomy, laser conization) that will be efficacious while allowing maximum maintenance of anatomical integrity and functional activity of the reproductive, urinary, and gastrointestinal systems • Perform palliative surgery as indicated, eg, in event of intestinal obstruction
Sexual dysfunction ^d	<ul style="list-style-type: none"> • Prescribe pharmacologic treatment for surgery-related sexual disorders (eg, lubricating gels, hormone replacement therapy) • Recommend counseling and education about sexual dysfunction and available methods for improving sexual function • Hormone replacement therapy where appropriate. Can also suggest alternative therapies for menopausal symptoms, eg, homeopathic medications, herbal teas, vitamin E, soy-rich foods • For vaginal dryness, recommend use of lubricants (eg, K-Y[®] jelly, estrogen creams) • To prevent vaginal stenosis, recommend intercourse or use of vaginal dilator on a regular basis • Educate and counsel patient regarding sexual implications of her disease and its treatment, and methods to manage sexual difficulties. Nurses should consider use of PLISSIT model (Annon 1976) for guiding assessment and education of the patient • Basic nonpharmacologic treatment strategies: <ul style="list-style-type: none"> – Encourage stimulation and eliminate routine (eg, encourage use of erotic materials; encourage communication during sexual activity, recommend use of vibrators; discuss varying positions, times of day, or places) – Provide distraction techniques (eg, encourage erotic or nonerotic fantasy; recommend background music, videos, or television) – Encourage noncoital behaviors (recommend sensual massage, sensate-focused exercises) – Minimize dyspareunia (eg, vaginal lubricants, topical lidocaine; position changes [superficial: female astride; deep: position changes so that force is away from pain and deep thrusts are minimized]; warm bath before intercourse); Kegel exercises
Treatment-related toxicities	<ul style="list-style-type: none"> • Monitor for irreversible and cumulative effects, and adjust dosages and regimens as indicated • Consider supportive therapy with growth factors for myelosuppression

continued on next page

Table 1, *continued*

Factor	Treatment Strategy
Nausea/vomiting ^e	<ul style="list-style-type: none"> • Chemotherapy-related acute: <ul style="list-style-type: none"> – For patients receiving highly emetic cisplatin or noncisplatin chemotherapy, administer 5-HT₃-receptor antagonists plus a corticosteroid – For patients receiving agents with intermediate emetic potential, administer a corticosteroid – For patients receiving agents with low emetic potential, administer antiemetic as needed • Chemotherapy-related delayed: <ul style="list-style-type: none"> – For patients receiving highly emetic cisplatin chemotherapy, administer a corticosteroid with either a 5-HT₃-receptor antagonist or metoclopramide – For patients receiving highly emetic noncisplatin chemotherapy, administer a corticosteroid alone, or a corticosteroid with either 5-HT₃-receptor antagonist or metoclopramide – For patients receiving agents with intermediate emetic potential, administer antiemetic as needed – Consider administration of NK1 receptor antagonist • Chemotherapy-related anticipatory: <ul style="list-style-type: none"> – Use most active antiemetic regimen appropriate for the chemotherapy to be administered, and recommend behavioral therapy with systematic desensitization • Radiation-related: <ul style="list-style-type: none"> – High risk: a 5-HT₃-receptor antagonist with or without a corticosteroid – Intermediate risk: a 5-HT₃-receptor antagonist or a dopamine receptor antagonist – Low risk: antiemetic (dopamine or 5-HT₃-receptor antagonist) as needed • General: <ul style="list-style-type: none"> – Counsel patient regarding prevention of delayed nausea and vomiting, and need for strict compliance with self-administered antiemetics – Educate patient about potentially helpful behavioral interventions, eg, imagery, distraction, progressive muscle relaxation, music therapy, accupressure, diet modification
Neurotoxicity ^f	<ul style="list-style-type: none"> • Reduce dosage of neurotoxic agent, or switch patient to agent with low or no neurotoxic potential • In case of paclitaxel neurotoxicity, consider administration of glutamine or venlafaxine
Alopecia ^g	<ul style="list-style-type: none"> • Provide information about salient aspects of hair loss, eg, why and how this occurs, transience or irreversibility of the problem, how to minimize hair loss, possible effects on body image and sexuality • Where applicable, reassure patient about transient nature of this condition; recommend support group for patients undergoing cancer therapy • Teach self-care strategies, eg, protecting scalp from cold, sun, and mechanical irritation; massaging and applying cream/ointments to scalp to keep it soft and reduce itching • Assist with wigs and other cosmetic measures • Use of scalp hypothermia may be helpful, but is controversial, due to both safety and efficacy concerns
Anemia, anemia-related fatigue, and fatigue ^h	<ul style="list-style-type: none"> • Administer an rHuEPO (eg, epoetin alfa) when hemoglobin level falls below 10.5 g/dL (or earlier), and maintain the hemoglobin level at approximately 12 g/dL • Initiate discussions about fatigue to help patients understand the causes and treatments of this symptom • Selectively treat cause(s) of fatigue, eg, administer antidepressants or analgesics for depression or pain; rHuEPO for anemia; calcium, magnesium, or phosphorus for metabolic imbalances; also, recommend moderate exercise, and advise patient on planning activities and accompanying rest in order to reduce fatigue

^aLevy 1996; Ahmedzai 1997; Cherney 1997; Harper 2000; Walsh 2000; Gordin 2001

^bKomurcu 2000

^cVergote 2000; Pignata 2001

^dPhillips 2000; Wilmoth 2000; Brassil 2002

^eGralla 1999; Bender 2002

^fDunton 2002; Durand 2002; Peltier 2002

^gBatchelor 2001; Protière 2002; Ridderheim 2003

^hCurt 2000a

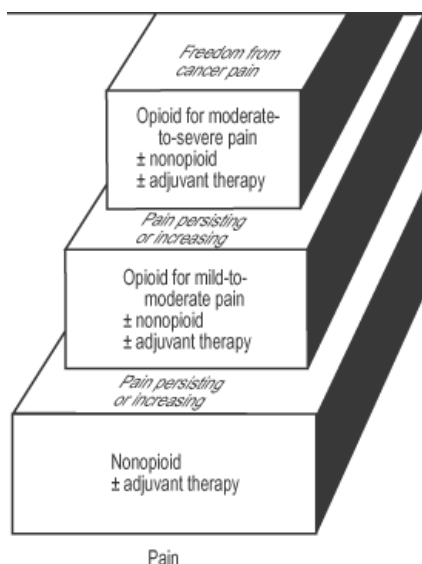


Fig. 1. Analgesic ladder (WHO 1990).

Comparison of patients who were using analgesics alone with those using a combination of nonpharmacologic strategies plus analgesics indicated similar pain-related outcomes, although there was a trend toward more positive effect in the group using combination therapy. The findings of this study highlight the need for healthcare providers (particularly nurses) to be aware of strategies their patients are using, to evaluate the effectiveness of these strategies, and, if effective, to encourage their use, with the goal of maximizing pain relief and enhancing QOL.

Emotional distress

Patients with gynecologic malignancies face an array of emotional challenges that can impair QOL, including anxiety, anger, guilt, and depression about their disease; concerns about changes in life patterns (eg, alteration in physical abilities, change in social relationships); and fear about pain, treatment effects, and loss of independence, as well as the very basic fear of death itself (Steginga 1997; Harper 2000; Howell 2003). Loss of sexual feeling and perceived loss of femininity also contribute to the list of negative emotional effects experienced in this patient population. In a French survey in which chemotherapy side effects were ranked by gender, women ranked “loss of hair” and “loss of sexual feeling” – two side effects that may be considered reflective of femininity and sexual identity – as second and fourth among the most severe side effects experienced (Carelle 2002). Another survey explored the difficulties considered to be priorities by gynecologic cancer patients ($n = 82$) at the time of diagnosis

and during treatment (Steginga 1997). The patients had been treated and were disease-free at their most recent outpatient visit to the treatment center. The most common difficulties reported by the patients with emotional difficulties were depression (49%), anxiety (37%), and fear of dying (35%), whereas fatigue (14%), pain (11%), and bladder dysfunction (9%) were the most commonly reported effects in patients with physical side effects; 13% of the patients described sexuality problems as their main difficulty at diagnosis and during treatment, with the main problems related to femininity issues (6%) and removal of reproductive organs. It is important to note that many of these issues persist 5 to 10 years after diagnosis (Wenzel 2002a,b), which reinforces the need to assess and treat problems early in the disease process.

Treatment

Anxiety, depression, and concerns related to perceived loss of femininity and sexual identity are common among gynecologic cancer patients. Some of these problems, at least in part, are managed in tandem with other problems; for example, relieving pain or addressing sexual dysfunction will have a positive impact on the patient’s emotional state and QOL. However, as a general measure, it is important for health care professionals to provide a supportive, empathic, nonjudgmental environment for the patient so she feels comfortable discussing her problems and expressing her feelings. Additionally, educational information, counseling sessions, and appropriate drug treatment (antidepressants, anxiolytics) should be considered (Komurcu 2000).

Surgery-related impairments

Surgery is not only a diagnostic tool, but in most cases is also the cornerstone of therapy for gynecologic malignancies (Pignata 2001). Fortunately, improvements in anesthesia and postoperative care over the last few decades have markedly reduced the morbidity and mortality of radical surgery in gynecologic cancer patients (Makar 1992). With this accomplished, attention is now turned to surgical procedures and practices that can more effectively enhance or preserve patient QOL while achieving disease-targeted goals (Vergote 2000; Pignata 2001).

Depending on the surgical procedure used and the cancer type treated, gynecologic cancer patients may experience an array of postsurgical QOL impairments that include loss of childbearing capacity, premature menopause, vaginal dryness, bowel or bladder dysfunction due to radical removal of innervated tissue or loss of

these functions due to pelvic exenteration, and poor cosmetic outcome (as may occur with radical vulvectomy) (Pignata 2001; Duffy 2001). Further, gynecologic surgery can be accompanied by significant blood loss (Hyllner 2002), necessitating blood transfusion, which in itself can cause a number of serious albeit infrequent side effects, as well as QOL deficits.

Treatment of gynecologic cancer in most cases is multimodal, involving chemotherapy or radiation therapy in addition to surgery, and patients may therefore experience QOL deficits reflective of all therapies used. Common acute side effects of chemotherapy typically include nausea and vomiting, alopecia, neuropathy, fatigue, and anemia, whereas those of radiation therapy include skin changes, nausea and vomiting, fatigue, anemia, bladder irritation, diarrhea, vaginal itching, burning, dryness, and loss of appetite.

Surgical advances

Advances in the surgical management of some gynecologic cancers are being made to reduce or minimize short- and long-term consequences, including those with implications for QOL. For example, a procedure has been introduced to help preserve the pelvic autonomic nerves during radical hysterectomy (Trimbos 2001). Damage to these nerves is believed to cause considerable morbidity, eg, impaired bladder function, defecation problems, and sexual dysfunction. The procedure, which incorporates elements of Japanese nerve-preserving techniques, involves identification and preservation of the hypogastric nerve in a loose sheath under the ureter and lateral to the sacro-uterine ligaments; lateralization of the inferior hypogastric plexus in the parametrium and avoidance during parametrial transection; and preservation of the most distal part of the inferior hypogastric plexus during dissection of the posterior part of the vesico-uterine ligament. This procedure appears both feasible and safe, but long-term survival and relapse data must be awaited. Also, radical hysterectomy was previously recommended for all patients with any degree of invasive cervical cancer. More recently, however, cone biopsy alone has become a therapeutic option for young patients with stage IA₁ disease who wish to preserve fertility, an important QOL consideration since patients with early cervical cancer are often young and have not achieved their reproductive goals (Morris 1996; Rose 2000). Another good example is the designation of combined modality therapy for patients with locally advanced cervical cancer (Stages Ib, IIb, III, and IVa) – once not widely accepted – as the standard of care. This change occurred as a result of three well-conducted studies that compared radiation

therapy alone or radiation therapy plus hydroxyurea with concurrent radiation plus cisplatin-based chemotherapy (Keys 1999; Morris 1999; Rose 1999). All three studies demonstrated significantly greater improvement with the radiation/cisplatin-based chemotherapy combination. Based on these findings, the National Cancer Institute recommended the addition of concurrent cisplatin-based chemotherapy to radiation therapy for women requiring radiation therapy for cervical cancer (Thomas 1999). {However, the long-term morbidity and side effects of such combinations still await a thorough evaluation.}

In the ovarian cancer setting, cytoreductive surgery followed by chemotherapy is considered standard treatment for patients with advanced disease (Pecorelli 2002b). Interval debulking surgery, a procedure in which surgery is preceded and followed by chemotherapy, has been suggested as a palliative measure that may confer a survival benefit. In an EORTC trial, interval cytoreduction improved survival by one third in advanced ovarian cancer patients (van der Burg 1995). The Gynecologic Oncology Group (GOG) further explored this procedure and, in contrast, found no improvement in overall survival for patients with advanced suboptimal ovarian carcinoma who had previously undergone maximal ovarian cytoreductive surgery (Rose 2002). Aside from questions regarding the efficacy of interval debulking, there is some concern about possible morbidity, QOL detriments, and patient acceptance because of the need for two surgical procedures within a short time, and evaluation of the procedure continues (Wenzel et al. in press). One of the most remarkable and welcome advances has been in vulvar cancer surgery. Previously, patients with advanced vulvar cancer underwent radical vulvectomy and pelvic exenteration including removal of the anus, lower rectum, or bladder, depending on tumor involvement, as well as en bloc dissection of the labia minora, labia majora, clitoris, and inguinal-femoral lymph nodes. The patient was left with a high risk of wound separation and infection, and poor cosmetic results. Today, surgery is usually limited to ipsilateral wide local resection with retention of as much normal tissue and function as possible, and removal of lymph nodes by separate incisions, optimizing wound closure (Plante 2000). Also, preoperative chemotherapy and radiation therapy are used to shrink the tumor, decreasing the extent of required surgery and potentially enhancing patient outcome and QOL. Additional surgical and combined modality strategies that may better preserve fertility (eg, radical trachelectomy in cervical cancer, hormonal treatment of early endometrial cancer, conservative surgery for early-stage epithelial ovarian cancer, novel assisted reproductive technologies

for patients facing loss of ovarian function), reduce the use of mutilating or more radical forms of surgery, or otherwise improve patient QOL are currently being evaluated. Radical trachelectomy, initially received with skepticism when introduced in 1994, is gradually gaining recognition and acceptance (Plante 2000). Briefly, the procedure comprises an initial laparoscopic pelvic lymphadenectomy, followed by trachelectomy provided lymph nodes are negative and a clear endocervical margin of 5 to 8 mm can be obtained; otherwise, a complete vaginal radical hysterectomy is performed. With the more conservative procedure, the cervix, although shorter, has a relatively normal appearance and results regarding obstetrical outcome have been encouraging.

Depending on the surgical procedure used and cancer type treated, blood loss can be significant. Thus, one of the basic steps in managing gynecologic cancer patients is to minimize any surgery-related blood loss. Prior to the 1990s, a large blood loss during surgery was treated with blood transfusion. The availability of rHuEPO provides another therapeutic option. To reduce the need for transfusion, presurgical autologous blood donation is becoming more common. Results of several studies have indicated that rHuEPO effectively increases red blood cell mass when administered preoperatively to patients scheduled for autologous blood donation prior to surgery, suggesting that this agent may be helpful in maintaining hemoglobin at levels high enough to permit the collection of a sufficient amount of blood within a short period (Goldberg 1997; Hyllner 2002).

Sexual dysfunction

Sexual dysfunction is common in gynecologic cancer patients, and may be due to physiologic, anatomic, or psychological factors, or a combination of these factors. Oophorectomy results in the loss of ovarian estrogen and testosterone production, both of which are needed to regulate female sexual function. Loss of estrogen can lead to hot flashes, vaginal dryness and atrophy, urinary incontinence, depression, and loss of libido, whereas loss of testosterone leads to loss of appetite, energy, memory, libido, orgasm, and genital sensation (Brassil 2002). Thus, premenopausal gynecology cancer patients who undergo oophorectomy, like postmenopausal women, can experience a hormone-related decrease in vaginal lubrication and subsequent dyspareunia, decreases in desire, lack of arousal, and difficulty achieving orgasm. Orgasm is mediated by stimulation of the pudendal or pelvic nerves, and damage or destruction of these nerves during surgery can impair women's orgasmic

ability (Wilmoth 2000). Further, chemotherapy or pelvic radiation therapy often affects ovarian function, resulting in decreases in sexual desire and orgasm (Brassil 2002). In addition, following pelvic radiation or intracavitary radiation, the vaginal tissue may become fibrous as the scarring process begins, with a resultant loss of the tissue's ability to stretch during intercourse (Wilmoth 2000). This, in turn, can further sexual dysfunction.

A patient's self-esteem may be eroded by loss of reproductive function, disfiguring surgical treatment (eg, radical vulvectomy), cosmetic issues (eg, neovagina), and radiation- or chemotherapy-related alopecia. In turn, the loss of self-esteem can adversely affect sexual response, as well as the patient's intimate relationship with her sex partner. It has been shown that women with a more negative sexual self-view show greater sexual morbidity following cancer than do women with a more positive self-view (Andersen 1999). Other psychological factors that may interfere with sexual response are stress and depression (with or without anxiety), which can lead to decreased desire, arousal, and orgasm, as well as fatigue, which may leave the woman too exhausted to participate in sexual activity (Wilmoth 2000; Brassil 2002).

Treatment

Currently, many pharmacologic and nonpharmacologic options are available for female cancer patients experiencing sexual dysfunction. Where appropriate, hormone replacement therapy may be administered, although this is determined by the type and stage of the disease (Wilmoth 2000; Brassil 2002). Vaginal dryness may be ameliorated by use of lubricants (eg, water-soluble moisturizers, jellies, vitamin E oil or suppositories, estrogen cream, tablets or rings). Vaginal stenosis commonly occurs as a result of radiation therapy but can usually be prevented by use of a vaginal dilator or by having intercourse on a regular basis. Maintenance of vaginal patency is important not only to preserve sexual function, but also to permit adequate follow-up pelvic examinations. Patient education and counseling (preferably involving both partners) are very important components of managing sexual dysfunction in gynecologic cancer patients. Effective holistic care requires informing the patient about the basic concepts of female sexuality, patient history and physical examination techniques, the impact of her disease and its treatment on sexual function, and pharmacologic approaches to managing problems related to sexual function (Phillips 2000). Additionally, patients should be informed about nonpharmacologic treatments (including behavior modification) that are available for enhancing sexual function (eg, changes in the environment, timing, and methods of lovemaking; Kegel exercises).

Chemotherapy- and/or radiotherapy-related impairments

Many currently used first- and second-line chemotherapeutic agents can induce significant toxicities, some cumulative or irreversible, that can potentially diminish QOL and even compromise long-term treatment or re-treatment (McGuire 1996; Groopman 1999; Keys 1999; Coiffier 2001; Armstrong 2002; Dunton 2002). For example, platinum compounds, the mainstay of treatment for most gynecologic malignancies (Pignata 2001), are associated with cumulative myelosuppression (particularly granulocytopenia and thrombocytopenia), neurotoxicity, and nephrotoxicity, as well as severe noncumulative toxicities including anemia and nausea/vomiting (Groopman 1999; Armstrong 2002; Dunton 2002). Neurotoxicity, anemia, and nausea/vomiting all have well-known adverse effects on QOL.

Drug toxicity problems may also be induced or exacerbated by the use of multidrug therapy or multimodal therapy that may include radiation therapy and one or more chemotherapeutic agents (Rose 1999; Keys 1999; Seiden 2001). Paclitaxel in combination with a platinum compound is now considered the standard of care as first-line chemotherapy for advanced ovarian cancer (McGuire 1996). However, paclitaxel has a number of toxicities (eg, granulocytopenia, anemia, thrombocytopenia) that overlap those of the platins, and the co-administration of paclitaxel and a platinum compound can potentially increase the frequency and/or severity of shared toxicities. Additionally, paclitaxel itself is associated with peripheral neuropathy, which can add to the disease burden of the cancer patient (Cella 2003b; Seiden 2001). In a study of multimodal therapy, radiation therapy in combination with cisplatin alone, cisplatin plus fluorouracil and hydroxyurea, or hydroxyurea alone was assessed in women with locally advanced cervical cancer (Rose 1999). Both cisplatin groups achieved gains in overall survival and progression-free survival; however, patients who received radiation therapy plus the three-drug regimen experienced more leukopenia and other hematologic effects of both Grade 3 and Grade 4 toxicity than did patients in the other two groups ($P < 0.001$).

It is imperative that clinicians be aware of the most important toxicities and side effects associated with the major chemotherapeutic agents used, so that these may be prevented or treated, in an effort to optimize QOL and total patient care. Table 2 lists specific side effects of several commonly used therapies reported in four studies in patients with gynecologic malignancies. In three studies, the most frequently reported side effects

of Grade 3 and Grade 4 severity were hematologic, whereas in the fourth study, the most frequent Grade 3–4 side effect was alopecia (Grade 3 only). In two other studies, Grade 3 and Grade 4 hematologic side effects again predominated; prevalence rates in the first study were 37% for high-risk cervical cancer patients receiving radiation therapy plus chemotherapy versus 1% for those receiving radiation therapy only (Morris 1999), and in the second study were 78% (leukopenia) for patients with platinum-refractory ovarian cancer treated with paclitaxel (Trimble 1993).

Nausea and vomiting

Nausea and vomiting are among the treatment side effects most feared by patients undergoing chemotherapy or radiation therapy (Markman 2002; Schnell 2003). Uncontrolled, these symptoms can substantially diminish QOL of patients, their families, and caregivers. Additionally, the distress associated with nausea and vomiting can lead to patients' refusal to continue with optimum anticancer therapy (Doherty 1999; The Italian MC Group 1999; Hesketh 2000). Treatment-related nausea and vomiting are also viewed by clinicians with some apprehension, as these symptoms can cause physical damage, including Mallory-Weiss tears of the esophagus, and can induce a number of potentially life-threatening complications including dehydration and electrolyte imbalance (Schnell 2003).

Chemotherapy-associated nausea and vomiting are generally categorized as acute (beginning within 24 hours after the start of chemotherapy and lasting for several hours) (Schnell 2003), delayed (beginning more than 24 hours after the start of chemotherapy and persisting for up to 6 or 7 days) (Yalcin 1999; Hesketh 2000), and anticipatory (beginning before, during, or after chemotherapy administration, but before acute symptoms would be expected to occur, and typically associated with a previous episode of poorly controlled vomiting during prior chemotherapy) (Gralla 1999; Yalcin 1999; Markman 2002; Schnell 2003). These distinctions among the various types of chemotherapy-related nausea and vomiting are crucial, as they determine the type of antiemetic therapy required. Importantly, it appears that good control of acute nausea and vomiting, particularly during initial treatment of chemotherapy-naïve patients, correlates with the control of delayed (and anticipatory) symptoms during the first chemotherapy cycle, as well as acute, delayed, and anticipatory nausea and vomiting during subsequent treatment cycles (Roila 1991; Italian Group 1992; Roila 1993).

Table 2
Grades 1–2 and 3–4 toxicities during treatment (% of patients)

Reference	Indication	Toxicity	Treatment (Grade 1–2)		Treatment (Grade 3–4)	
Cantu (2002)	Recurrent ovarian cancer		PAC (n=47)	CAP (n=47)	PAC (n=47)	CAP (n=47)
		Leukopenia	NA	NA	4	34
		Neutropenia	NA	NA	13	36
		Thrombocytopenia	NA	NA	0	13
		Nausea/vomiting ^a	17	51	0	0
		Alopecia ^b	87	60	0	0
		Allergic reactions ^b	15	2	0	0
		Sensory neuropathy ^c	11	6	0	0
		Myalgia ^d	19	4	0	0
Keys (1999)	Stages III & IV ovarian cancer		RT+CIS (n=183)	RT alone (n=186)	RT+CIS (n=183)	RT alone (n=186)
		Hematologic	56	18	21	2
		GI	58	24	14	5
		Genitourinary	31	19	2	3
		Cutaneous	14	9	0	2
		Neurologic	8	0.5	1	0.5
McGuire (1996)	Stages III & IV ovarian cancer		CIS+CYC (n=201)	CIS+PAC (n=184)	CIS+CYC (n=201)	CIS+PAC (n=184)
		↓ WBCs or neutrophils	13 ^f	6 ⁱ	83 ^f	92 ⁱ
		↓ Platelets	46 ^g	49 ^j	3 ^g	3 ^j
		Anemia	53 ^h	58 ^k	8 ^h	<9 ^k
		GI	60	56	11	15
		Fever	11	16	0	<4
		Alopecia	37	63	e	e
		Renal	5	3	<2	<1
		Neurologic	16	24	4	4
		Allergic	1	4	0	4
Papadimitriou (1999)	Stage IV or recurrent uterine cervix carcinoma			CIS+PAC (n=34)		CIS+PAC (n=34)
		Granulocytopenia		30		15
		Anemia		60		18
		Thrombocytopenia		0		3
		Alopecia		9		88
		Nausea/vomiting		73		9
		Renal		18		0
		Hepatic		0		0
		Stomatitis		15		0
		Diarrhea		12		0
		Neurotoxicity		44		9
		Myalgias/arthralgias		12		0
Allergy		3		0		

Abbreviations: CAP, cyclophosphamide, doxorubicin, cisplatin, CIS, cisplatin, CYC, cyclophosphamide, NA, not available (only maximum severity given), PAC, paclitaxel, RT, radiation therapy.

^agrade 2–3

^dgrade 2

^gn = 198

^jn = 180

^bno grade given

^eseverity graded as 0, 1, or 2

^hn = 200

^kn = 182

^c≥grade 2

^fn = 197

ⁱn = 179

Treatment

Modern treatment of nausea and vomiting is based on the results of a large number of clinical antiemetic trials conducted during the 1980s and 1990s in patients with a broad range of cancers, including gynecologic malignancies. At present, the serotonin (5-HT₃) receptor antagonists are considered the “gold standard” for antiemetic therapy in high and moderate emetic-risk cases (Gralla 2002, Schnell 2003). These agents are highly effective in preventing the nausea and vomiting induced by most chemotherapy regimens (including cisplatin) and by radiation therapy (Gralla 1999). Four 5-HT₃-receptor antagonists are currently available, granisetron, ondansetron, and dolasetron, all of which are approved for use in the USA and Europe, and tropisetron, which is approved for use in Europe and several non-European countries. The individual 5-HT₃-receptor antagonists appear to have comparable efficacy and thus can be used interchangeably, based on convenience (Gralla 1999). Despite the efficacy of the 5-HT₃-receptor antagonists, a substantial proportion of patients undergoing chemotherapy still experience acute nausea and vomiting, depending on the regimen used (Heron 1995). Thus, the 5-HT₃-receptor antagonists are frequently administered in combination with corticosteroids, usually dexamethasone or methylprednisolone, for the treatment of acute chemotherapy-induced nausea and vomiting. In general, 5-HT₃-receptor antagonists are less effective in preventing delayed symptoms than acute symptoms, and corticosteroids, either alone or in combination with a 5-HT₃-receptor antagonist or metoclopramide, are currently recommended for delayed vomiting in high emetic-risk situations; however, no regular prophylactic use of antiemetics for delayed vomiting is suggested for patients receiving intermediate- or low-risk chemotherapeutic agents (Gralla 1999). Results of a very recent trial in gynecologic cancer patients have suggested that a “cocktail” of granisetron, methylprednisolone, and droperidol may be more effective than either granisetron alone or a granisetron/methylprednisolone combination in controlling delayed and/or anticipatory vomiting resulting from cisplatin-based chemotherapy (Sagae 2003). Further, several recent clinical trials have suggested that a new class of agents, neurokinin-1 (NK1) receptor antagonists, may be particularly effective in preventing delayed nausea due to highly emetogenic chemotherapy (Navari 1999; Van Belle 2002; Chawla 2003).

Evidence-based guidelines, such as those developed by the American Society of Clinical Oncology (ASCO), the Multinational Association of Supportive Care in Cancer, and the European Society for Medical Oncology, are

currently available to assist physicians in selecting appropriate antiemetic therapies based on specific clinical circumstances (Gralla 2002; Schnell 2003). Broadly, these guidelines are based on the results of published clinical trials, and provide recommendations for most clinical settings. Overall, clinical experience clearly indicates the need for early and successful prophylaxis of treatment-related nausea and vomiting (Gralla 1999; Schnell 2003). Not only should antiemetic therapy be provided during the period of hospitalization, but it should also be made available for any ambulatory patient at risk of delayed vomiting during the posttreatment period. Additionally, patients should be counseled regarding the importance of preventing emergence of delayed nausea and vomiting, and their need for strict adherence to self-administered antiemetic regimens. Such measures can help decrease hospitalization and time in the ambulatory setting, enhance the patients' QOL, and possibly lead to better compliance with future antineoplastic therapy.

A number of nonpharmacologic therapies can also be used to treat nausea and vomiting when standard antiemetics are ineffective. Among these therapies are hypnosis, relaxation techniques, behavioral modification, guided imagery, and distraction. However, these therapies appear to be more effective in treating anticipatory than acute or delayed nausea and vomiting (Tabano 2002).

Neurotoxicity

Neurotoxicity, particularly peripheral neuropathy, is an important side effect induced by chemotherapeutic agents commonly used in the gynecology setting including the platinum compounds, taxanes, and vinca alkaloids. Depending on the agent used, peripheral neuropathy may primarily involve large-fiber sensory nerves, which control vibration and position sense, or both large- and small-fiber sensory nerves, the latter controlling touch, pain, and temperature sensations; however, motor nerves may also be affected (Sweeney 2002).

Cisplatin, which affects the large sensory nerve fibers, initially causes sensations of burning, tingling, and numbness in the fingers and toes; impaired vibratory sense; and hypersensitivity to pain. The neuropathy may progress to diminished deep tendon reflexes with impairment of position sense, sensory ataxia, and neuropathic pain; however, gross motor function is preserved. Peripheral neuropathy usually develops when cumulative doses exceed 400 mg/m², and in patients given high doses (>500 mg/m²), symptoms may continue to worsen after cisplatin withdrawal (Sweeney 2002;

Plotkin 2003). Cisplatin also commonly causes ototoxicity, with permanent high-tone hearing loss reported in up to 45% of patients receiving this agent (Adams 1989). Carboplatin has activity similar to that of cisplatin, but is less neurotoxic. Peripheral neuropathy has been reported only rarely and these cases occurred in patients who had previously received high-dose cisplatin therapy and had experienced mild neuropathy (Heinzlef 1998; Plotkin 2003). Paclitaxel, which mainly affects the small sensory nerve fibers, is associated with an especially high incidence of neurotoxicity, ie, more than 50% of patients who receive doses exceeding 250 mg/m² develop significant neuropathy (Cella 2003b; Plotkin 2003). Rapid-onset sensory neuropathy can occur, particularly with high-dose regimens, and, as indicated earlier, the use of this agent may be limited by cumulative peripheral neurotoxicity, which can severely impact the patient's QOL (Gordon 1997; Dunton 2002; Calhoun in press). Symptoms include a decrease in pain and temperature sensation (small fiber) as well as loss of vibration and position sense, deep tendon reflexes, muscle strength, and fine motor movement (large fiber). Peripheral neuropathy is increased when paclitaxel is given with cisplatin, given in doses greater than 200 mg/m², or given to patients with pre-existing conditions such as diabetes mellitus or alcoholism, or when high cumulative doses are administered. The symptoms often improve after discontinuation of treatment (Plotkin 2003).

Treatment

Patients at risk of chemotherapy-associated neuropathy must be carefully monitored during the entire course of treatment, with lowering of the dosage, or discontinuation of the chemotherapeutic agent and replacement with another agent having less or no neurotoxic potential. Recent reports indicate that administration of glutamine or the antidepressant venlafaxine may be helpful in cases of paclitaxel-induced neuropathy (Durand 2002; Peltier 2002), and that amifostine may provide protection from cisplatin-induced neuropathy (Santini 1999); however, at present there appears to be no drug available to reliably prevent or cure chemotherapy-induced neuropathy (Quasthoff 2002). Nonpharmacologic approaches to treatment of chemotherapy-induced neuropathy are based on patient education about potential neuropathic side effects, impact of these side effects on performance of daily activities (eg, buttoning clothes, walking, sensing control pedals while driving, checking water temperature), and related safety issues. Although little published information is available for patients, an educational booklet on peripheral neuropathy sponsored by the Memorial

Sloan-Kettering Cancer Center has been written and may be obtained from patients' physicians or nurses, or via the Internet (Almadrones 1999). The booklet provides salient information on peripheral neuropathy and its management, with an emphasis on safety issues, as well as sources of information and referrals that may aid patients experiencing this complication.

Alopecia

Alopecia occurs in both men and women undergoing chemotherapy or radiation therapy. Alopecia has been described as the most disturbing anticipated side effect by up to 58% of women scheduled for chemotherapy (McGarvey 2001). Chemotherapy-associated alopecia develops most frequently with doxorubicin, cyclophosphamides, and the taxanes/taxoids (Khayat 2000), and is the only cumulative toxicity reported during long-term topotecan therapy (Möbus 2001). Hair regrowth generally begins about 1 to 2 months after cessation of chemotherapy, but this interval is less predictable following radiation therapy (Khayat 2000).

Treatment

Alopecia, although a common and troublesome side effect of chemotherapy and radiation therapy, is best managed by providing information to help the patient prepare for sudden hair loss (thus minimizing the negative impact on the patient's self-image), and, where appropriate, reassuring the patient that this is a temporary condition that will be reversed on cessation of therapy. Other support measures involve counseling, teaching self-care strategies to cope with the physical aspects of alopecia, and assisting with wigs and other cosmetic measures (Batchelor 2001).

Anemia and fatigue

Anemia is a common side effect of cancer and its treatment, occurring in more than 50% of patients at some time during the course of their disease (Bron 2001). To obtain a clearer picture of the incidence and importance of anemia in cancer patients, the European Cancer Anemia Survey (ECAS) was conducted between January and July 2001 to obtain definitive data on the prevalence and incidence of cancer-related anemia, risk factors for its development, and anemia treatment practices. Of 15,367 patients enrolled, 1,741 had gynecologic cancer (Schrijvers 2003). At enrollment, 49% of evaluable gynecologic cancer patients were anemic (hemoglobin level <12 g/dL). This percentage increased to 81% during the survey period; however, only 43% of the anemic patients

received anemia treatment. These results show anemia to be an important but undertreated complication in gynecologic cancer patients in Europe (Schrijvers 2003). In a U.S. study that retrospectively investigated anemia in patients who had undergone radiation therapy between December 1996 and June 1999 (Harrison 2002b), the prevalence of anemia in patients with uterine/cervical cancer was 75% at baseline and 79% by the end of treatment.

Anemia can cause a broad range of symptoms that negatively affect QOL, including fatigue, tachycardia, palpitations, dyspnea, dizziness, malabsorption, decreased libido, and cognitive deficits (Ludwig 2001). Further, results of numerous studies suggest that anemia may have a negative impact on outcome in cancer patients independent of its impact on QOL. In patients with gynecologic malignancies treated with chemotherapy, radiation therapy, or chemoradiotherapy, anemia (or a low hemoglobin level) has been identified as a negative prognostic factor for survival and disease control, and, in some cases, a negative predictive factor for response to treatment (Eisenhauer 1997; Obermair 2001; Harrison 2002a; Marinaccio 2002; Muenstedt 2002).

Fatigue is the most common symptom reported by cancer patients (Portenoy 1994), having an estimated prevalence of about 78% (Vogelzang 1997; Curt 1999; Curt 2003). Like anemia, fatigue can profoundly affect QOL (Cella 1998; Groopman 1999; Portenoy 1999b; Sobrero 2001; Campos 2002). Concomitant conditions that may contribute to fatigue include infection, dehydration, sleep disorders, pain, depression, and anxiety; however, anemia is often the major contributing factor (Campos 2002).

In a recent presentation at the American Society of Clinical Oncology (2002), a significant correlation was reported to exist between greater decreases in hemoglobin levels and increases in fatigue interference with QOL ($r = -0.32$, $P = 0.05$) (Jacobsen 2002). In several earlier studies, relationships were demonstrated between hemoglobin levels and both fatigue and nonfatigue items on QOL scales (Cella 1997; Littlewood 2001). In a multicenter, randomized, double-blind, placebo-controlled study in which epoetin alfa, a recombinant human erythropoietin (rHuEPO), was administered to patients with anemia who were receiving nonplatinum chemotherapy, results of univariate analysis showed a strong and statistically significant (range, $P = 0.0002$ to $P = 0.0325$) correlation between change in hemoglobin level and change in QOL for all primary variables evaluated, ie, FACT-G, FACT-An Fatigue subscale, the Cancer Linear Analog Scale (CLAS) items Energy Level,

Ability to Do Daily Activities, and Overall QOL, and the Short Form 36 (SF-36) Physical Component Summary and Mental Component Summary (Littlewood 2001).

The clinical implications of fatigue for QOL in cancer patients have been examined in several surveys (Vogelzang 1997; Curt 1999; Curt 2000a; Curt 2000b; Curt 2000c; Curt 2003). Overall, these surveys demonstrated that fatigue is associated with significant physical, emotional, psychological, social, and economic consequences, adversely affecting virtually every aspect of the patient's daily life, as well as taking a toll on the lives of the patient's primary caregivers (Figs. 2 and 3). Importantly, one survey demonstrated some major differences in perceptions of fatigue between the

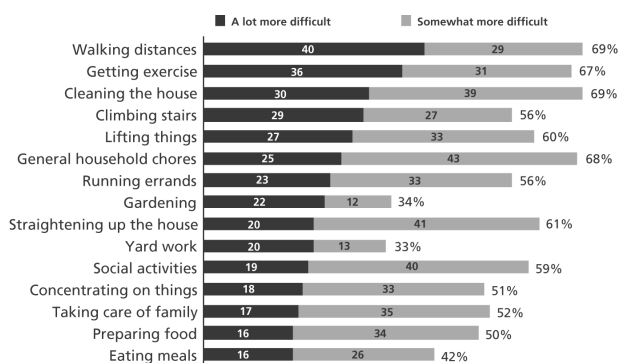


Fig. 2. Daily activities that were "a lot" or "somewhat" difficult for $\geq 50\%$ of cancer patients ($n = 301$) when experiencing fatigue (Curt 2000c).

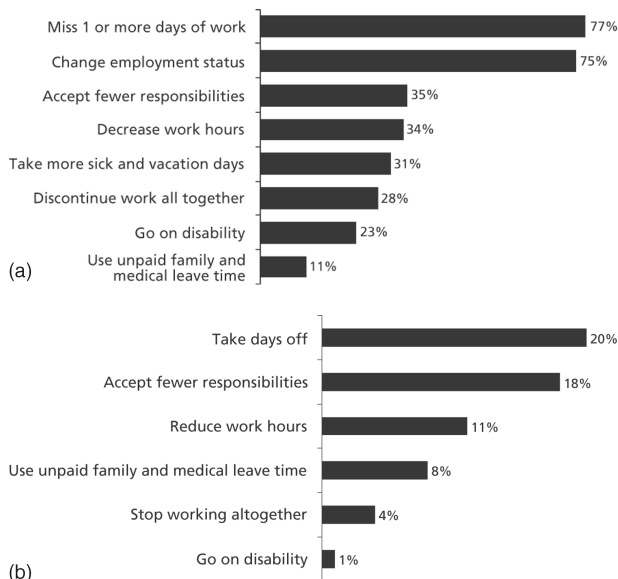


Fig. 3. (a) Occupational effects of fatigue reported by cancer patients working at the time of diagnosis ($n = 177$) (Curt 2000c). (b) Occupational impact of the patient's cancer treatment on primary caregivers ($n = 301$) (Curt 2000c).

patients and their health care providers (usually physicians) (Vogelzang 1997). Particularly noteworthy was the finding that 61% of patients felt that fatigue affected their lives more than cancer-related pain, whereas only 37% of oncologists held this view. Also, the surveys highlighted the lack of communication about fatigue between patients and their health care providers, and the general lack of recommended treatment for this incapacitating condition.

Treatment

Because of the association among fatigue, anemia, and low hemoglobin levels, one can logically assume that

correction of the patient's anemia may concomitantly provide a benefit regarding fatigue, which has implications for QOL. Numerous placebo-controlled and open-label studies have shown that improvement in QOL can be achieved by correction of anemia with epoetin alfa (Glaspy 1997; Demetri 1998; Gabrilove 2001; Littlewood 2001; Crawford 2002; Fallowfield 2002; Lahousen 2002; Campos 2003; Cella 2003a; Shasha 2003). Results of both univariate and multivariate analyses of data from a double-blind, placebo-controlled trial that included 375 patients with nonmyeloid malignancies showed that administration of epoetin alfa three times weekly resulted in significant (all, $P < 0.04$) improvement in the CLAS items Energy Level, Ability to Do Daily Activities, and Overall QOL; the FACT-G; and the Fatigue subscale of the FACT-An (Fig. 4) (Littlewood 2001; Fallowfield 2002). Three large, open-label, community-based studies that evaluated the QOL effects of epoetin alfa three times weekly or once weekly provided further evidence of a beneficial effect of this agent on QOL in patients receiving chemotherapy (Glaspy 1997; Demetri 1998; Gabrilove 2001). Retrospective analysis of the data for a subgroup of gynecologic cancer patients ($n = 297$) from one of the studies ($N = 2370$) (Demetri 1998) that used a three-times-weekly epoetin alfa regimen (Campos 2002) also showed significant ($P < 0.001$) improvement from baseline for QOL measures (Energy Level, 33% improvement; Ability to Do Daily Activities, 34% improvement; Overall QOL, 27% improvement). Categorization of QOL response by change in hemoglobin level showed that the greatest improvements in QOL were seen with the greatest increases in hemoglobin (Fig. 5) (Campos

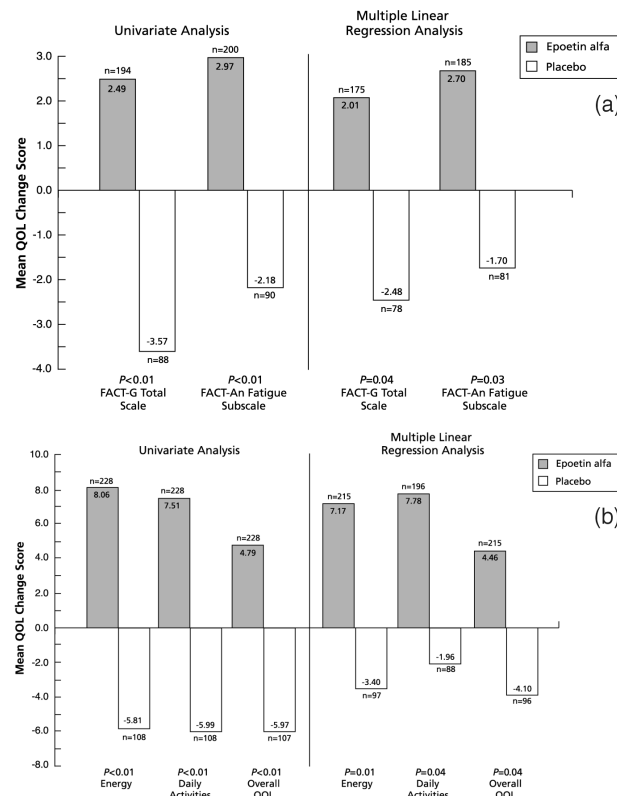


Fig. 4. (a) Comparison of QOL mean change scores for epoetin alfa- and placebo-treated patients: results of univariate (Littlewood 2001) and multivariate analyses (FACT-G Total score and FACT-Fatigue subscale). Positive scores represent improvement; negative scores represent deterioration. Differences between the treatment groups were significant for all QOL scales. P values adjusted for multiple comparisons using sequentially rejective Bonferroni procedure (Fallowfield 2002). (b) Comparison of QOL mean change scores for epoetin alfa- and placebo-treated patients: results of univariate (Littlewood 2001) and multivariate analyses (CLAS items Energy Level, Ability to Do Daily Activities, Overall QOL). Positive scores represent improvement; negative scores represent deterioration. Differences between the treatment groups were significant for all QOL scales. P values adjusted for multiple comparisons using sequentially rejective Bonferroni procedure (Fallowfield 2002).

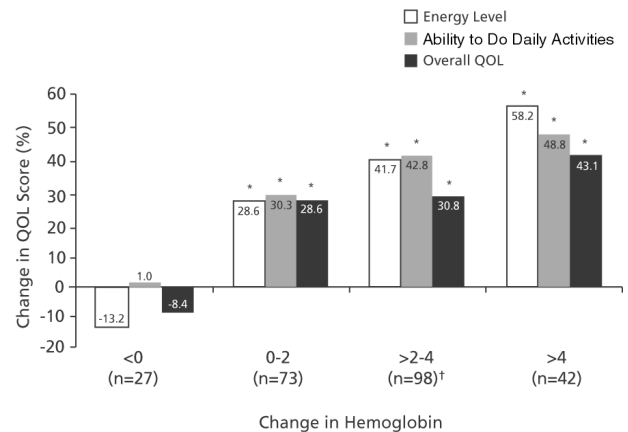


Fig. 5. Change in QOL compared with change in Hb for patients with gynecologic malignancies. Mean change in scores were significant ($P < 0.001$) for all domains (energy [white bars], ability to do daily activities [gray bars], and overall QOL [black bars]) as Hb increased, with greatest QOL improvements seen with the greatest increases in Hb. [†] $n = 97$ for overall QOL (Campos 2002).

Table 3
Recommendations for use of erythropoietic therapy in anemic cancer patients receiving chemotherapy

ASCO/ASH recommendations (Rizzo 2002) Epoetin alfa	NCCN recommendations (NCCN 2003) ^a	
	Epoetin alfa	Darbepoetin alfa
Criteria for initiation		
Hemoglobin <10 g/dL	Hemoglobin <11 g/dL	
In certain clinical circumstances if Hb is 10–12 g/dL	Under certain circumstances, immediate treatment may be required; in this event, blood transfusion should be administered	
Starting dose		
150 IU/kg three times weekly	150 IU/kg (10,000 IU) three times weekly	2.25 µg/kg once weekly
OR	OR	
40,000 IU once weekly	40,000 IU once weekly	
Dose escalation		
Dose escalation to 300 IU/kg three times weekly for an additional 4–8 weeks in those not responding to initial dose at week 4 ^b	Dose escalation to 300 IU/kg (20,000 IU) three times weekly or 60,000 IU weekly if no response at 4 weeks ^b	Dose escalation to 4.5 µg/kg weekly if no response at 6 weeks [†]
Dose titration		
Dose titration to maintain Hb around 12 g/dL	Dose titration to maintain Hb at 12 g/dL	
Discontinuation		
Discontinue after 6–8 weeks if there is no response (<1–2 g/dL increase in Hb)	Discontinue if, after dose escalation, Hb level has not increased by 1 g/dL	
Discontinue if Hb >12 g/dL	Hold if Hb level exceeds 13 g/dL	
Restart when level falls to near 10 g/dL	If Hb falls to <12 g/dL, restart with a 25% reduction in dose	
	If dose causes a rapid response rate (Hb increase >1 g/dL in a 2-week period), continue therapy with a 25% reduction in dose	If Hb increases by more than 1 g/dL in a 2-week period, or if Hb exceeds 12 g/dL, continue therapy with a 25% reduction in dose
Iron repletion		
Baseline and periodic monitoring of iron, total iron binding capacity, transferrin saturation, or ferritin levels and instituting iron repletion when indicated may be valuable in limiting the need for rHuEPO ^c	If transferrin saturation <20% or serum ferritin level <100	

Abbreviation: Hb, hemoglobin

^a NCCN Guidelines, August 2003

^b Dose response defined as an increase in Hb of ≥ 1 g/dL.

^c The guidelines note that there is inadequate evidence to specify optimal timing, periodicity, or testing regimen for such monitoring.

2002). Similarly, a retrospective analysis of the data for a subgroup of ovarian cancer patients from the once-weekly epoetin alfa study showed significant ($P < 0.017$) improvement in QOL measures (Campos 2003). In all four studies (as well as in the retrospective subset analysis of gynecologic cancer patients [Campos 2002]), the change in Overall QOL correlated significantly with the change in hemoglobin level (range, $P = 0.0002$

to $P < 0.001$) (Glaspy 1997; Demetri 1998; Gabrilove 2001, Littlewood 2001, Campos 2002). These findings provided evidence that increasing hemoglobin levels by administration of epoetin alfa can significantly improve several aspects of QOL, including fatigue. Additional studies, including one that utilized minimally important difference (MID) analysis (Patrick 2003) and another that used a normative data comparison (Cella 2003a,

Cella 2003c), confirmed the clinical relevance of the observed effects of epoetin alfa on QOL in the double-blind, placebo-controlled study, including those related to the FACT-An Fatigue and Anemia scales.

Based on the positive findings of numerous clinical trials of erythropoietic stimulating agents, as well as concerns about the use of blood transfusion, erythropoietic stimulating agents are being used with increasing frequency to treat anemia related to cancer or its treatment. Thus, considerable efforts are currently being directed at establishing guidelines for optimal administration of these agents, eg, those recommended by the American Society of Clinical Oncology/American Society of Hematology (Rizzo 2002) and the National Comprehensive Cancer Network (NCCN) (NCCN 2003)¹, as well as by the participants in the Italian Gynecological Consensus Conference (Pecorelli 2002a). Broadly, the guidelines recommend the use of erythropoietic stimulating agents as a treatment option for patients with chemotherapy-associated anemia characterized by Hb levels ranging from <11 g/dL to <10 g/dL. The majority of anemic gynecologic cancer patients in clinical trials ($n \approx 1200$) were treated with epoetin alfa, which demonstrated an increase in hemoglobin and improvement in QOL parameters (Taylor 1998, Lahousen 2002, Blohmer 2003, Campos 2003). ASH/ASCO and NCCN guidelines for cancer- or treatment-related anemia in patients undergoing chemotherapy are summarized in Table 3. Efforts are continuing to identify new dosing schedules and regimens of erythropoietic agents that could offer additional benefits regarding patient convenience, rapidity of response, or other factors that will optimize anemia management (Chap 2002; Crawford 2002; Lahousen 2002; Patton 2002).

PATIENT EDUCATION AND SUPPORT MECHANISMS

Gynecologic cancer can be particularly distressing for patients, both physically and emotionally, due to the aggressiveness of the surgical and medical treatment administered, treatment-related side effects experienced, fears about disease recurrence or death, and changes in life-style necessitated by the disease. In a study of 161 long-term (5-10 years post-diagnosis) gynecologic cancer survivors, approximately 57% retrospectively stated that they desired counseling at the time of diagnosis, and 48% reported that they currently would be interested

in a support program. When queried about what would have been helpful at the time of diagnosis, 15% of respondents reported that they desired more medical information and education from their doctors, and 20% would have welcomed help in communicating better with doctors and nurses. These data suggest that efforts must be made by the patients' medical care providers to furnish a comprehensive care program that will help the patients move through the trajectory from diagnosis to recovery. Components of this program should include both patient and family education and psychosocial support. Specifically, efforts should be made to educate patients about the natural history of their disease and treatment options available, anticipated responses to treatment, and probable side effects, so that they can be more actively involved in treatment decisions, have more realistic expectation for outcome, and be better prepared to meet the challenges that lie ahead (Armstrong 2002; Howell 2003).

Psychosocial support should encompass a broad range of services such as emotional, nutritional, genetic, and financial counseling; steering patients and their families to institutional and community resources (eg, patient and family/caregiver support groups, workshops, advocacy groups); and providing referrals to organizations that offer general cancer information and support (eg, the American Cancer Society, the National Ovarian Cancer Coalition, CancerCare, Gilda's Club, Cancer Wellness Center, CancerBACUP, Ovacom). Supportive care for the entire family is an important aspect of patient care, as individual family members may need guidance in dealing with the changes in the family structure, interpersonal relationships, and care of the gynecologic cancer patient. Continuing evaluation of QOL is also important both to facilitate the recovery process and to ensure that the patients are receiving timely treatment and services.

CONCLUSION

The gynecologic cancer patient faces many challenges specific to the type of tumor and its treatment, as well as those common to the general oncology population. Among the many challenges are treatment toxicities and side effects that can significantly diminish QOL, as well as the decreases in QOL intrinsic to the disease itself. Alleviation of these negative events can play a crucial role in enhancing or preserving the patient's QOL during and after treatment, enabling her to withstand

¹ All guidelines are under continuous review and subject to change. Please refer to www.NCCN.org.

and complete the most effective therapy. Caring for the patient, as well as her cancer, requires that measures to preserve or enhance the quality as well as the quantity of life are incorporated into the patient's treatment plan. Future FIGO reports that address tumor site-specific QOL issues in gynecologic cancer patients are planned.

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