EXPERT REVIEWS

Supportive care for women with gynecologic cancers

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Supportive care is a multidimensional field, that involves caring for a patient's symptoms either during and/or after treatment. Ideally, once these supportive care needs are met, patients can enjoy an improved quality of life. Supportive care needs include all body systems, and are, therefore, difficult to manage, secondary to the fact that they require collaboration among multiple medical specialties. In this review, several components of supportive care are separated into two categories: tumor-related morbidities and treatment-related morbidities. Some of the themes discussed include nausea and vomiting, cancer pain, psychological distress, fatigue and anemia, small bowel obstruction and peripheral neuropathy. While all of these components are challenging to manage, it is perhaps the psychosocial realm that remains the most unmet need. Regardless, the oncologist must act as a facilitator who addresses these needs and, if unable to address the issue alone, knows how to steer the patient toward the appropriate provider. As these needs are met, the goal is for quality of life to improve; and with the improvement in quality of life we may expect to see improved survival outcomes.

KEYWORDS: gynecologic oncology • quality of life • supportive care

Overview of goals of supportive care

As progression-free survival and, in some cases, overall survival for many gynecologic malignancies continues to improve, providers and patients are more frequently faced with the challenges of supportive care. Supportive care has been defined as treatment given in order to prevent, control or relieve complications and side effects, as well as improve the patient's comfort and/or quality of life (QoL) [1,101]. It is a multidimensional field that addresses two main adverse effects – tumor-related effects and treatment-related effects (TABLE 1). Tumor-related morbidities affect a patient's comfort and QoL, thus requiring supportive care. The tumor itself may be the cause of pain, malnutrition, bowel obstruction, ascites and pleural effusion. Conversely, treatment-related morbidities are the unfortunate, but occasionally severe, iatrogenic-induced sequelae associated with therapy. Supportive care in this category addresses peripheral neuropathy, nausea and vomiting, anemia and fatigue, depression and anxiety, and sexual dysfunction. These categories are not mutually exclusive, but assignment of these morbidities into two groups provides a framework through which one may begin triaging the supportive care needs of gynecologic oncology patients.

The rationale for improvement in supportive care is to enhance the QoL for patients experiencing the effects of cancer during treatment, progression, remission, palliation or after cure. Therefore, the goals of supportive care should be directed at addressing symptomatology in all organ systems so as to aid in a patient's tolerance of all aspects of cancer treatment. This tolerance directly affects QoL, which has been defined as a patient's unique perception of how the disease and its treatment affect her overall sense of well-being [101]. By simultaneously addressing the multiple components of supportive care, gynecologic cancer patients may experience their treatment course differently. Furthermore, in future, as more patients are living with or without evidence of disease, oncologists will need to address issues in supportive care on a more frequent basis. This review highlights several aspects of supportive care as they pertain to the patient with gynecologic cancer.

Tumor-related morbidities

Pain

Pain is one of the more common but perhaps frequently untreated symptoms in cancer patients [2]. As opposed to nausea and vomiting, unfortunately patients and their caregivers may choose to

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suffer the consequences of not treating pain in order to avoid the side effects and addictive properties of opioids [3–5]. As pain may be associated with the original diagnosis, the patient may associate recurrence of disease with pain and may, therefore, be reluctant to report such symptoms. This may lead to exacerbations and poor control in the chronic setting and poor management of cancer pain has been associated with decreased physical and emotional status [4,5,101]. Therefore, it is critical that pain should not be suffered and that significant attention to its management is paid in order to improve overall QoL.

There is concern that, as the life expectancy of patients increases, cancer will become a chronic illness requiring special attention to chronic pain and disability [6]. Pain during diagnosis and treatment is perhaps distinct from pain experienced by those patients in remission. Finally, pain control in palliative care may be approached differently, with specific considerations in the hospice-type setting. It is important to recognize that the control of pain in the acute setting may serve as a preventative measure for the development of a chronic pain syndrome [6].

Providing education, both in the inpatient and outpatient setting, serves to improve patient satisfaction, as well as control of pain [7]. Oncologists and their patients should understand the ability of poorly controlled pain to affect other aspects of supportive care which influence QoL. For example, untreated pain may result in insomnia and fatigue. Pain can be classified into three types, and this classification system may help guide treatment during and/or after adjuvant therapy: visceral pain is poorly localized, may refer to a cutaneous region and is dull or colicky. It may present itself in the setting of a bowel obstruction; neuropathic pain is prolonged, severe, burning and may be associated with such symptoms as sweating or tachycardia, which may be seen following radiation or surgical injury; and, finally, somatic pain is described as tender, localized to the site of injury, constant, throbbing or aching, typically seen in bone metastasis [8,9].

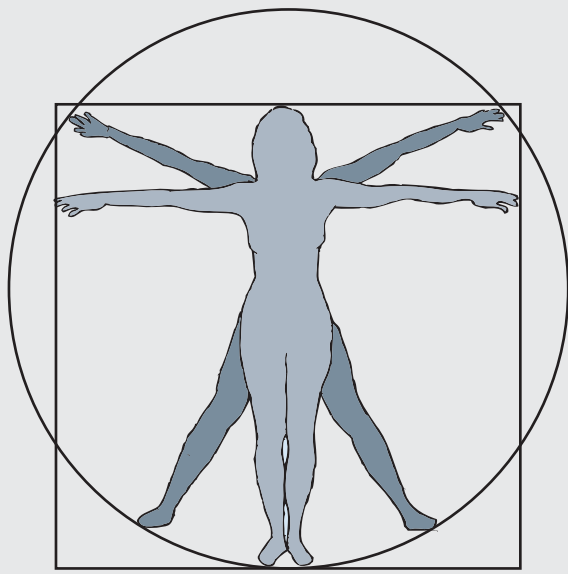
In any of the above types of pain, the World Health Organization (WHO) advocates following a management ladder with initiating treatment with NSAIDS, followed by the addition of opioids [102]. The WHO advocates the use of the ladder as a guideline with the understanding that each case should be managed individually. It is important to consider that patients tolerate opioids differently and, furthermore, patients should enter into the ladder scheme depending on the level of their pain. When using opioids, the provider might consider concomitant use of an NSAID, such as ibuprofen, as either drug alone is not as effective as the combination [9]. The most common opioids used in cancer patients are listed in Table 2. Short-acting opioids should be chosen initially, followed by longer acting medication, such as fentanyl or oxycodone. It is important to schedule opioid use, rather than prescribing opioids on an as-needed basis, because exacerbations of pain are more difficult to treat [9]. One may be optimistic that a carefully planned, yet simple, opioid regimen may successfully control cancer pain in 80–90% of cases [10]. Unfortunately, opioid use is not without side effects, which often complicate management and require further alterations in supportive care. For example, the control of constipation and/or nausea resulting from opioid use requires special attention and, likely, additional prescriptions (Table 2).

Cachexia & malnutrition

Cachexia is defined by Femia *et al.* as loss of over 5% of bodyweight over 2–6 months [11]. Cachexia is related to nutritional status. The cancer itself causes metabolic alterations, such as increased muscle protein breakdown and glucose metabolism

Table 1. Treatment- and tumor-related effects of gynecological cancer.

Treatment-related effects	Tumor-related effects
• Nausea and vomiting	• Pleural effusion
• Peripheral neuropathy	• Small bowel obstruction
• Anxiety and depression	• Cachexia and malnutrition
• Sexual dysfunction	• Ascites
• Anemia and fatigue	• Pain



while the treatment of cancer affects appetite and food intake. The literature supports the notion that the patient's body habitus, and therefore QoL, is altered by these changes [12]. Furthermore, it is evident that malnutrition contributes to poor outcome in gynecologic oncology patients [13]. Clearly, oncologists need to be aware of the implications of malnutrition in patients receiving therapy, as poor nutritional status may negatively affect a patient's response to therapy, as well as QoL during therapy [13].

Nutritional support using dietary supplements and shakes (e.g., Ensure®), along with the oncologist's attention to this issue, may improve the response to treatment for some patients (Table 3). Nutritional counseling, oral nutritional supplementation, and home parenteral nutrition (HPN) have also been linked to improved QoL [13]. Finally, while appetite stimulants, such as megestrol acetate (Megace®), are thought to improve cancer-related anorexia–cachexia, they have not been shown to affect survival and/or global QoL [14,15]. Interestingly, Megace is thought to be more effective than either eicosapentaenoic acid (alpha 3-omega fatty acid) or marijuana derivatives; and only corticosteroids are as effective as Megace [15]. Unfortunately, Megace carries the risk of venous thromboembolism (VTE), perhaps as high as a sixfold increase, thus limiting its use in the gynecologic oncology patient population [16].

Oncologists and patients may differ when it comes to nutrition and hydration in the supportive and/or palliative care setting. Brown *et al.* found that the majority (63%) of patients would like nutrition and hydration to be continued even though the use of respiratory supports, such as oxygen or ventilators, might be limited [17]. The authors state that patients may not consider nutritional support 'heroic'. Even though patients might not agree with discontinuation of nutritional support, the management of malnutrition in the palliative setting remains controversial. For example, although total parenteral nutrition (TPN) or HPN is considered, by many, to be unnecessary in terminally ill patients, there is some evidence that it has a positive impact in certain patient populations, including patients with a life expectancy of greater than 3 months [18,19]. TPN carries its own risks and discomfort; therefore, strong QoL studies need to address this issue.

Table 2. Common oral and transdermal opioid medications for the treatment of cancer-related pain.

Generic name	Trade names
Opioid medications	
Morphine sulfate	MSIR®, Roxanol™
Oxycodone	Percocet™, Percodan®
Hydromorphone	Dilaudid®
Meperidine	Demerol®
Methadone	Dolophine®
Oxycodone controlled release	Oxycontin®
Morphine sulfate controlled release	MS contin®, Oramorph™
Fentanyl	Duragesic®
Medications to treat and/or avoid opioid-related constipation [85]	
Magnesium citrate	Citroma®
Lactulose	
Senna (good first-line choice)	Senekot®
Docusate sodium	Colace™
Bisacodyl	Dulcolax®

Pleural effusion

Dyspnea is the subjective feeling of respiratory distress and, thus, is often an interplay between anxiety and hypoxia from tumor burden. Some have suggested that supportive care of this symptom should include the provider's ability to address the patient's subjective breathlessness [11]. As dyspnea may indicate poorer prognosis and shorter interval to death, addressing this symptom is paramount to enhancing QoL in the time period near death [20].

Ripamonti *et al.* suggest that dyspnea may result from a combination of three different complications: first, obstructive pathology such as pleural effusions; second, cancer cachexia, or malnutrition and weakness; and, third, an increase in ventilator requirements, such as metabolic acidosis or anemia [20]. Gynecologic oncologists most frequently encounter this tumor effect in ovarian cancer patients, as dyspnea can be secondary to pleural effusions (Table 4). It is suggested that thoracocentesis and chemical pleurodesis be reserved for palliative situations in which chemotherapy or other treatments are not likely to reverse the effusions. For symptomatic control, and/or when mechanical control of the pleural effusion is not an option, most advocate opioids and/or oxygen therapy. Benzodiazepines, as well as oxygen therapy, may also have a role in control of dyspnea, although evidence is lacking. Finally, some have advocated activity modifications to prevent the onset of dyspnea, which may involve caregiver instruction to tailor daily activities.

Ascites

Ascites is most frequently seen in the ovarian cancer population and often requires symptom alleviation via paracentesis. Although paracentesis is an invasive procedure with a relatively short-term benefit, it does address the patient's discomfort with abdominal distention and, to a lesser extent, the related insomnia, dyspnea and nausea [21]. There are, however, other therapies employed for symptom management, as listed in Table 4. Unfortunately, comparative data are lacking, especially when looking for measurements of QoL. Management approaches with diuretics, with or without serial paracentesis, versus permanent indwelling catheters are case-dependent [22,23]. A recent Phase I/II trial investigated the effect of monoclonal antibodies directed against ascites-specific malignant cells, and specifically

Table 3. Prevention and treatment of cancer-related cachexia.

Treatment	Comments
Nutritional counseling [13]	– Improves quality of life – Patients prefer face-to-face counseling
Oral nutritional supplements (ONS; e.g., protein shakes [Ensure®])	– Linked to improved quality of life when combined with other therapy
Corticosteroids [15]	– Dexamethasone 4 mg/day – Caution in elderly – Watch for side effects with long-term use
Megestrol acetate (Megace®) [14,15]	– 480–800 mg/day – Liquid form also available – Questionable effects on quality of life – Slight increase in deep venous thrombosis risk
Cannabinoids [15]	– Dronabinol and nabilone – Megace more successful at appetite stimulation and weight gain in randomized trial
Total parenteral nutrition or home parenteral nutrition [17–19]	– Debatable role in palliative care – May play a role in optimizing patient's nutritional status prior to therapy or surgery – Patients and caregivers may fear starvation at end of life – Monitor glucose and phosphate

epithelial cell adhesion molecule (EpCAM) on the surface of ascitic tumor cells, on the control of ascites; however, randomized controlled studies are still lacking [24]. Other approaches suggested include the use of VEGF antagonists to reduce ascites, as VEGF may be implicated in the formation of ascites by increasing vascular permeability [24].

Table 4. Management of pleural effusions and ascites.

Management	Comment
*Ascites**	
Diuretics	– Effective for 1/3 of patients – Renin/aldosterone ratio may be predictive of response – Suggest spironolactone at 150 mg/day, increasing dose until response (furosemide also an option)
Paracentesis	– Immediate symptom relief – Risks include infection, bowel perforation, hypovolemia – Safe up to 5 l, questionable usefulness of albumin or i.v. fluids – Limited duration of effect
Permanent drains	– Risk of peritonitis; may need prophylactic antibiotics; may last up to 8 weeks
Peritoneovenous shunts	– For refractory ascites, success shown for ovarian cancer patients – Continuous re-infusion of fluid from peritoneal cavity into SVC – Procedure associated with numerous complications such as DIC
New therapies	– VEGF inhibitors – Matrix metalloproteinase inhibitors – Antibody therapy (catumaxomab)
Pleural effusions‡	
Symptom management	– Opioids – Home oxygen – Benzodiazepines
Thoracocentesis	– For slowly reaccumulating effusions – Risk of re-expansion pulmonary edema
Pleurodesis/ indwelling catheter	– For rapidly reaccumulating effusions – Requires hospitalization and chemical pleurodesis – Questionable improved control with indwelling catheter for patients with poor prognosis
Psychosocial modifications	– For palliative care, prevention of dyspnea (related to effusions) may involve activity modifications and the support of caregivers
Other	– May respond to chemotherapy in the case of ovarian cancer

*Adapted from [22].
‡Data from [20].
DIC: Disseminated intravascular coagulation; i.v.: Intravenous; SVC: Superior vena cava.

Small bowel obstruction

Bowel obstruction in gynecologic malignancy is problematic. It is particularly difficult to manage in the setting of recurrent disease and/or palliative care. Up to 42% of all patients with ovarian cancer will have an episode of bowel obstruction [25]. Bowel obstruction has an impact on QoL as the therapeutic options (surgical, medical or supportive) are challenging for the patient. For those with terminal disease, one must select a therapeutic modality that will alleviate discomfort while, at the same time, minimizing suffering in the remaining weeks or months of the patient's life.

There is a fair representation of various treatment options in the literature. A retrospective study found that surgery carries a higher morbidity, although chemotherapy and surgery had similar outcomes in terms of reobstruction [26]. Of particular interest, conservative management alone has much earlier reobstruction rates. Many have attempted to define the prognostic factors that predict benefit after surgery; some of the key factors include: age over 65 years, nutritional status, tumor burden, rapidly reaccumulating ascites, poor nutritional status, carcinomatosis, previous chemotherapy for recurrence, and radiation therapy to the whole intestine. Krebs and Gopelrud used a predictive index by scoring patients with a value of 0, 1 or 2 in six of the above categories, and found that patients who scored higher than six had a worse outcome with surgery (Figure 1) [26]. However, if surgery is chosen, the patient must understand that the probability of living with an ileostomy in roughly 50%, with potential ensuing complications of fistula(s) for the balance of the patient's life [27,28]. In a study by Mangili *et al.,* only surgical treatment was a prognostic factor for improved survival; however, it is likely that those patients who were offered surgery had other qualities, which predisposed them to improved survival [25].

In inoperable cases, or situations where the patient and/or oncologist decide to proceed with medical or conservative management, several options exist. A percutaneous endoscopic gastrostomy allows patients to hydrate themselves by mouth [28]. By decreasing intestinal secretions, octreotide has improved QoL and decreased hospitalization [27]. Moretti *et al.* used temporary nasogastric drainage, with simultaneous use of octreotide, antiemetics and analgesics in a terminal patient [29]. Critical in their algorithm is fluid management, as they stress the importance of keeping daily water intake between 0.5 to 1.5 l. In the last month of the patient's life,

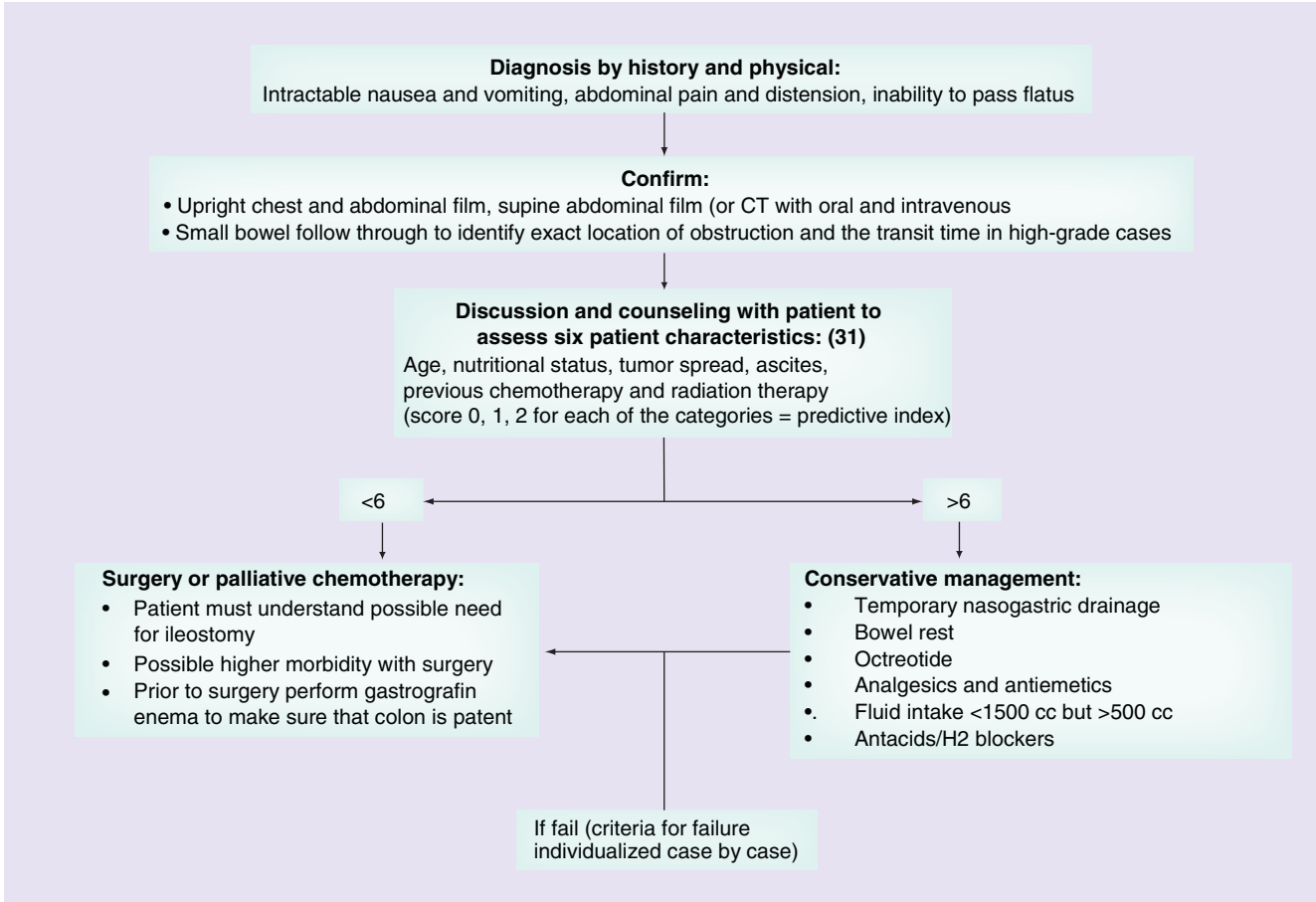


Figure 1. Management of small bowel obstruction.
Data from [26].

this combined medical and conservative approach decreased pain, nausea, dry mouth, thirst, dyspnea, feeling of abdominal distention and drowsiness in the palliative setting.

Other tumor-derived considerations

Table 5 provides a summary of additional supportive care issues in the realm of tumor-related effects. First, it is critical to provide venous thromboembolism (VTE) prophylaxis to patients with gynecologic cancer, in order to prevent the high morbidity and mortality associated with VTE. The incidence of VTE in this patient population can approach 20%, and is likely secondary to the older age of patients, the radical surgical procedures, and the mechanical effects caused by pelvic tumors. It has even been suggested that in the ovarian cancer population, VTE is a risk factor for decreased survival [30]. The best method of prophylaxis remains debatable. Prophylaxis with sequential compression devices, unfractionated heparin, or low-molecular-weight heparin, is recommended [31].

Second, when addressing 'tumor fever', it is critical to rule-out other causes of cancer-related fever. It is suggested that tumor fever may be more responsive to NSAIDs than to acetaminophen, and that this regimen is less likely to be associated with chills or tachycardia [32]. Zell and Chang have proposed an algorithm to manage tumor fever: work-up for infectious etiology; while awaiting diagnostic test results, treat empirically with antibiotics; if tests return negative for infection, initiate treatment with naproxen; if defervescence occurs, assume tumor fever; if no deffervescence, then treat for occult infection [32]. They suggest that Naproxen has a more rapid onset of action than other NSAIDs.

Finally, bone metastases are a frequent cause of cancer-related pain and therefore warrant discussion here. The management of this type of pain is unique, and symptoms should be managed appropriately. Radiation therapy is indicated in this setting for the palliation of pain caused by metastasis. A recent meta-analysis looked at the ongoing debate for the use of single versus multiple fractions, and concluded that the two treatment modalities are equivalent in terms of pain relief, although re-treatment is higher in the single fraction group [33]. Bone metastases are also important in the case of hypercalcemia, and are certainly a frequently encountered issue in supportive care. The approach to this issue is detailed in Table 5.

Treatment-related morbidities

Chemotherapy-induced nausea & vomiting

Nausea and vomiting tend to be the most feared symptom related to cancer treatment [34]. Chemotherapy-induced nausea and vomiting (CINV) may occur in 70–80% of patients receiving chemotherapy [35]. Even after antiemetic therapy, patients prefer to experience other toxicities and side effects rather than withstand nausea and vomiting [36]. CINV can be divided into four subcategories: the National Comprehensive Cancer Network (NCCN) defines acute nausea as that occurring shortly after chemotherapy administration, but resolving within the first 24 h. Delayed nausea occurs after 24 h, peaks between 48–72 h, and resolves by the 6–7th day [103]. Anticipatory nausea is described as a learned or conditioned response prior to chemotherapy; and, finally, breakthrough CINV can occur when a patient experiences symptoms despite appropriate therapy [35].

There are basically three main classes of drugs used to treat CINV: 5-hydroxytryptophan (5-HT) serotonin receptor antagonists, corticosteroids and aprepitant, a neurokinin-1 receptor antagonist. The American Society for Clinical Oncologists (ASCO) recently updated their guidelines for the use of

Table 5. Other components of tumor-related supportive care.

Effect	Comment
Tumor fever	– Naproxyn for diagnsosis and treatment (375 mg every 12 h) – Other NSAIDs may not be as effective – Important to rule-out and treat infection
Bone fracture and hypercalcemia of malignancy	– Monitor serum calcium – Hydration and thiazide diuretics – Bisphosphonates (pamidronate, zoledronic acid) for treatment and prevention – Radiation therapy for bone metastasis
Ureteral obstruction	– Ureteral stent – Percutaneous nephrostomy
Thrombocytosis and hypercoagulability	– Likely prophylaxis for all gynecologic oncology patients – Heparin, low-molecular-weight heparin (Lovenox®), sequential compression devices
Large bowel obstruction	– May be managed conservatively in patients with competent ileocecal valve if the cecum is not dilated >8 cm – Colonic stent versus transverse loop colostomy versus end colostomy with Hartmann pouch
Bleeding and the management of fungating masses	– Palliative radiation therapy to the pelvis for persistent cervical bleeding (ten fractions of radiation therapy) in patients receiving chemotherapy for distant metastasis

antiemetics in oncology; their recommendations, with some additions, are detailed in Table 6 [37,38]. All have a high therapeutic index for CINV, and should be considered as first-line therapy [38]. 5-HT receptor antagonists, in addition to dexamethasone and aprepitant, are indicated for the control of CINV in high-dose chemotherapy regimens. There are several 5-HT serotonin receptor antagonists, all with similar therapeutic and side-effect profiles. There is some suggestion that palonosetron performs superior to other agents in this class; nevertheless, further studies are warranted. Aprepitant (Emend), a neurokinin-1 receptor antagonist, is the newest agent, and has an important role in both acute and delayed CINV. For breakthrough CINV, the following agents may be considered when first-line therapeutics fail: metoclopramide, phenothiazines, butyrophenones and cannabinoids. Specifically, the cannabinoids, dronabinol and nabilone, both approved by the US FDA, are indicated for refractory CINV and, despite dysphoric side effects hindering their prescription, patients have been shown to prefer the use of these agents for subsequent chemotherapy cycles [39,40]. In anticipatory CINV, the most important concept is the prevention of acute and delayed emesis with the above drugs. However, ultimately when one is faced with controlling anticipatory CINV, benzodiazepines and behavioral therapy are suggested. Finally, if CINV proves to be refractory to all aforementioned treatment modalities, one must consider other etiologies for nausea and vomiting.

Lastly, an important concept in CINV is the selection of therapy based on the risk assessment of the chemotherapeutic agents used, a concept highlighted in the recent ASCO guidelines. The emetogenicity of antineoplastic drugs is separated into four categories: high, moderate, low and minimal risk. For example, a high-risk drug, such as cisplatin, requires treatment with 5-HT receptor blockers, dexamethasone and aprepitant, followed by dexamethasone and aprepitant for delayed CINV. Low emetogenic drugs (e.g., paclitaxel) may only require dexamethasone without additional agents for delayed CINV.

Anemia & fatigue

Fatigue is perhaps the most common symptom experienced by gynecologic cancer patients. Several factors are implicated in the causes of fatigue; for example, anemia, pain, nutrition, insomnia and psychological distress [41]. Fatigue has been reported by gynecologic patients as severe, distressing and uncontrollable [42]. Perhaps this is the result of inadequate attention on the part of healthcare professionals, coupled with a patient's reluctance to discuss their fatigue [42].

Insomnia plays a central role in cancer-related fatigue [43]. In a study of approximately 1000 patients, the onset of insomnia was reported to occur within the first 18 months after diagnosis [42]. Many reported the insomnia secondary to pain, thoughts and concerns, which investigators speculate may be addressed by psychosocial interventions and adequate pain relief. 25% of patients in this report used sleeping medications. Further investigations are needed for the appropriate diagnosis and treatment of cancer-related fatigue, especially in the realm of treatment-related insomnia and psychosocial intervention.

Treatment-induced anemia predisposes patients to cancer-related fatigue. As compared with other cancers, gynecologic cancers are especially known for being associated with severe anemia, in many cases with hemoglobin levels less than 9.9 [44]. Not only does anemia have a significant correlation with poor performance status [45], but it may be implicated in tumor sensitivity to radiation and chemotherapy [42,46]. It has been suggested that an optimal oxygen level for tumors to respond to therapy is reflected by a hemoglobin level between 12 and 14 g/dl [46].

Table 6. Treatment of chemotherapy-induced nausea and vomiting.

Class/receptor		Example	
Benzodiazepine/inhibits GABA		Ativan® (lorazepam)	
5-HT serotonin receptor antagonists		Zofran® (ondansetron)	
Substance P/neurokinin 1 receptor antagonist		Emend® (aprepitant)	
Corticosteroids/unknown antiemetic mechanism		Dexamethasone	
Anticipatory	**Acute**	**Delayed**	**Breakthrough/refractory**
– Benzodiazepines – Limited efficacy: guided imagery, music therapy, muscle relaxation, psychoeducational support and information – No proven efficacy: hypnosis, exercise, massage, aromatherapy, herbal remedies	– For high emetic risk regimens*: 5-HT3 receptor antagonist (Aloxi®, Zofran®) plus dexamethasone plus aprepitant (Emend®) – For moderate emetic risk: 5-HT3 receptor antagonist plus dexamethasone	– Cisplatin and all other high emetic risk*: dexamethasone plus aprepitant	– Do not use as first line*: methoclopramide, phenothiazines, butyrophenones and cannabinoids
Limited efficacy‡: guided imagery, music therapy, muscle relaxation; psychoeducational support and information.			
No proven efficacy‡: hypnosis, exercise, massage, aromatherapy, herbal remedies.			

* From American Society of Clinical Oncology Guideline for Antiemetics in Oncology: Update 2006 [38].
‡[37].
5-HT: 5-hydroxytryptamine; GABA: γ-aminobutyric acid.

Blood transfusion is an option for the treatment of cancer-related anemia; however, transfusions are associated with poor outcomes and QoL, due to infections, allergies and/or dependence on medical centers. For these reasons, many practitioners rely on growth factors, including epoetin alfa (rHuEPO; Epogen or Procrit®) or darbepoetin alfa (Aranesp®) to treat anemia (Figure 2) [47]. Kurz *et al.* concluded that rHuEPO increases hemoglobin levels and decreases transfusions in patients with gynecologic malignancies undergoing polychemotherapy, without compromising QoL [48]. It has even been suggested that rHuEPO may be given prophylactically in older patients (>65 years) and those with baseline hemoglobin of less than 10.5 who are going to be given chemotherapy consisting of carboplatin and paclitaxel [49,50]. While Aranesp has a longer half-life and, therefore, may be given at shorter intervals, there are few clear advantages compared with Procrit [51].

Unfortunately, this therapy is not without risks and there are concerns that the risk of VTE is increased for these patients [52]. It remains unclear whether the survival advantage with rHuEPO use is great enough to counterbalance its VTE risk. QoL effects must also be taken into account.

Peripheral neuropathy

An important component of supportive care is addressing the unfortunate, but often severe, iatrogenic-induced symptoms associated with treatment. Women with gynecologic malignancies who are treated with cisplatin- or taxane-based regimens are at risk for developing peripheral neuropathy. A subset of QoL questions related to neurotoxicity exist (the Functional Assessment of Cancer Therapy – Gynecologic Oncology Group – Neurotoxicity [FACT/GOG-Ntx]); these detail the sensory, hearing, motor and dysfunctional components of this symptom complex [53]. The FACT/GOG-Ntx exemplifies how providers may measure QoL for research, as well as practice purposes, by targeting a specific set of questions. Grade 2–3 sensory neuropathy and, less commonly, motor neuropathy, occur in 25% of patients receiving cisplatin or taxane-based regimens [53]. The most common complaints are reported to be burning dysesthesias, numbness and tingling and shooting in the distal extremities [54]. It has also been suggested that up to 23% of patients may suffer from residual peripheral neuropathy 48 months after treatment, thus presenting a potential obstacle to using this regimen in the recurrent setting [54]. Some authors have suggested predicting this side effect with a careful peripheral nerve exam, specifically targeting deep tendon reflexes and changes in vibration sensitivity [44].

Neuropathic pain resulting from peripheral neuropathy does not respond as well to opioids, and may require other management strategies, which employ antidepressants or anticonvulsants (Table 7) [55]. Preventative therapies have also been investigated, but with questionable success rates. Amifostine, a drug that could be given in tandem to chemotherapy, has been suggested to be neuroprotective; however, in clinical trials, as well as a recent Cochrane review, its effect was variable and, ultimately, had modest to no preventative effect [56,57]. Furthermore, amifostine has the potentially concerning side effects of severe nausea, vomiting, hypotension and allergy. Although oral vitamin E has been reported to reduce the incidence of neurotoxicity by 50%, these studies included only small sample sizes, and had other problematic methodology issues [57–59].

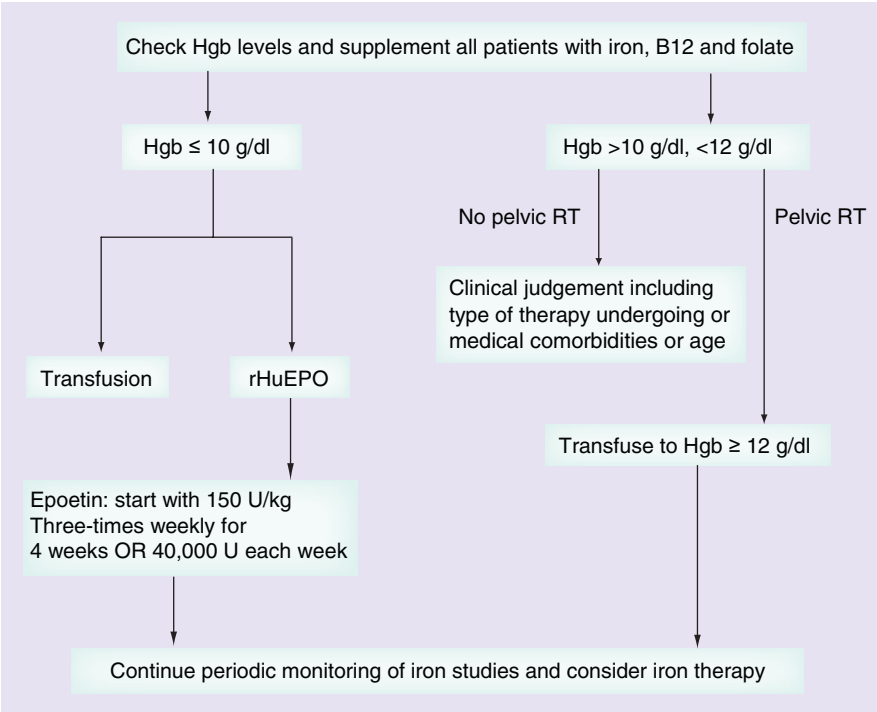


Figure 2. Treatment of chemotherapy-related anemia (based on American Society for Clinical Oncologists guidelines, 2002 [47]).
Hgb: Hemoglobin; rHuEPO: Recombinant human erythropoietin; RT: Radiation therapy.

Sexual dysfunction

Sexuality and body image are key factors affecting the QoL of women, especially after diagnosis and treatment of gynecologic malignancy. Sexual dysfunction in this patient population is complex and multidimensional, involving both emotional and physical limitations and insecurities [60]. It is concerning that women who were sexually active prior to diagnosis of a gynecologic malignancy frequently show sexual dysfunction for some time after treatment [60]. However, in a small study of 22 women with early-stage gynecologic cancers, three 1-h sessions of psychoeducational interventions were able to positively impact sexual functioning

Table 7. Prevention and treatment of peripheral neuropathy.

Treatment	Comments
Prophylaxis	
Amifostine [57,58]	– Modest neuroprotective effects in trials; dosing is premedicated chemotherapy with 740–910 mg/m^2 (500 mg/vial); can be associated with hypotension, severe nausea and vomiting, and allergy [86]
Vitamin E [59,87]	– Perhaps more promising effects than amifostine in prevention; 600 mg/day during chemotherapy and for 3 months after treatment is completed
Symptom management	
Gabapentin (Neurontin®)	– 300–1800 mg/day divided in three doses to treat symptoms; other potential agents include lamotrigine or topiramate
Antidepressants	– Tricyclic antidepressants also used to treat symptoms; of questionable efficacy
Acupuncture	– May ameliorate symptoms

and overall well-being [61]. This underscores the need for this type of intervention to help reverse the sexual dysfunction associated with treatment of these cancers.

Each type of gynecologic cancer has specific implications for sexual functioning. Cervical cancer and, particularly, the effects of radiation, have a specific impact on sexuality. Radiation-induced fibrosis of the vagina results in shortening and narrowing of the vagina. This effect, together with radiation-induced ovulatory failure, leads to vaginal dryness and, ultimately, dyspareunia. Vaginal dilation and estrogen creams are best employed early in the course of this complication. Unfortunately, without early intervention, the fibrosis may not be reversed; it is therefore critical for oncologists to ask about symptoms and prescribe dilators as early as possible. Hopefully, this is also being addressed by radiation oncologists. Unfortunately, this area has not been well addressed in the literature.

Hypoestrogenism after oophorectomy and/or chemotherapy and radiation also impacts sexuality. Although hormone therapy is a well-known and effective treatment for certain symptoms of hypoestrogenism, such as vaginal dryness and mood, oncologists and patients are reluctant to use hormone replacement therapy (HRT) in the setting of many gynecologic malignancies. The fear is that estrogen therapy may cause tumor growth, regardless of the QoL benefit that it might grant the patient. Insomnia and fatigue and, thus, depressive symptoms, are some of the effects of hypoestrogenism that have obvious implications on QoL. From a 2004 systematic review (although the data are limited in the setting of HRT use in ovarian cancer survivors vary, it appears that HRT is an acceptable treatment for menopausal symptoms [62]. A recent GOG study speculated that estrogen therapy is safe to use in women with early endometrial cancers, by showing low recurrence rates (2.1%) after therapy [63]. Unfortunately, definite recommendations regarding treatment of symptoms with estrogen cannot be made. Therefore, it is likely that a conversation between the provider and patient, considering symptoms and their effect on QoL, must direct therapeutic choices.

Anxiety & depression

The prevalence of depressive and anxiety disorders among women with gynecologic cancers approaches 50% [64]. In a study by Fowler *et al*, depressive and anxiety symptoms were high in women who had consulted a gynecologic oncologist (42 and 30%, respectively) [65]. The severity and prevalence of these psychological symptoms correlated highly with the number of gynecologic symptoms. Interestingly, older women, and those without a partner, were more likely to suffer from depression and anxiety.

The prevalence and severity of symptoms may fluctuate during the patient's treatment course. Chan *et al*. tracked the psychosocial state in gynecologic cancer patients to identify risk factors for maladjustment during treatment. While most patients adjusted well, in their sample of 74 women, those with lower socioeconomic status and those without family support or religious belief suffered more often from adjustment disorders [66]. Furthermore, pain, health-related QoL and poor performance status have been shown to affect these psychological disorders [67,68].

There is currently limited evidence available reporting on the pharmacological and psychosocial interventions used to treat in depressive disorders among cancer patients [69]. Four classes of drugs have been routinely used, including tricyclic antidepressants (TCAs), serotonin reuptake inhibitors (SSRIs), neuroleptics and benzodiazepines. It has been suggested that TCAs may be particularly helpful in patients with insomnia and cachexia, and that SSRIs may be indicated for patients with low energy, although the evidence regarding dosages and drug choice are heterogeneous [69]. The neuroleptics, such as haloperidol, or the benzodiazepines are not only indicated in patients with anxiety, but can also ameliorate nausea and vomiting simultaneously. Apart from medical therapy, it has been shown that actively seeking support for psychological concerns enhances QoL and mood [70]. It is not surprising that treatment of depressive and anxiety disorders in these patients might require medical therapy combined with such psychosocial therapy, as can be found in cancer support groups.

Table 8. Other considerations in treatment-related morbidities.

Effect	Comment
Alopecia	– Physical (such as hypothermia) and pharmacologic treatments with variable success, such as topical minoxidil (2% solution applied twice daily), which may shorten duration of alopecia related to certain chemotherapy agents [88]
Lymphedema [71,72]	– Lymphedema pumps, Jobst stockings, massage, daily antibiotic prophylaxis (Pen G™)
Infection	– Monitor absolute neutrophil count and temperature; consider growth factors (Neupogen®, Leukine®, Neulasta®), change Portacath®
Fistula	– Rectovaginal: blood transfusion, colostomy, fistula plug – Vesicovaginal: conduit – Enterocutaneous: bowel rest, total parental nutrition, H2 blockers, somatastatin
Stricture	– Colonic stent, diversion/colostomy
Loss of fertility	– Ovarian cortex cryopreservation, Lupron® during chemotherapy, surrogate uterus
Chemobrain [89]	– Not well understood, need more studies and standardized diagnostic test, consider renaming 'cancer-associated cognitive change'
Hypoestrogenism	– Premarin (plus Provera® if uterus present), soy products, black cohosh, bioidentical hormones

Other sequelae resulting from cancer therapy

The side effects of cancer therapy are the result of three different treatment modalities in gynecologic oncology, specifically, chemotherapy, surgery and radiation therapy. In addition to the principle treatment-related morbidities discussed above, there are other effects that should be addressed (Table 8). Specifically, lower extremity lymphedema can be burdensome and often difficult to control. In gynecologic oncology patients, both lymphadenectomy and radiation have a causative role in the development of lymphedema. Obesity may also predispose women to its development [71]. Lymphedema has an obvious impact on a woman's psyche: mobility becomes a challenge and body image is distorted, both of which lead to worsened QoL. Its prevalence in the gynecologic oncology population has been recently reported as 10%, with most cases being among vulvar cancer patients [72]. In the same study, most women reported using compression stockings, massage and exercises. The supportive care needs of these patients are high, and require special attention to physical needs and daily living, sexual needs, symptom management and education regarding the development of lymphedema. According to breast cancer literature, compression garments and massage are more effective than medical or other therapies in the control and relief of lymphedema [72].

Additional considerations

Impact of age & obesity

Two critical issues need to be discussed when considering the impact of comorbidities in our patient population on supportive care: obesity and older age. Both of these characteristics predispose gynecologic oncology patients to significant complications. Obesity is a well-studied risk factor that increases morbidity related to surgery and postoperative care. However, it is not clear why obesity predisposes both women with breast and colon cancer (and perhaps gynecologic malignancies) to worse survival outcomes [73]. Some speculate that this is related to inadequate dosing of chemotherapy, while others implicate hormonal effects brought about by circulating estrogen [73]. Unfortunately, the impact of obesity on adjuvant therapy in gynecologic cancers is not well understood. The influence and impact of obesity on the requirements for supportive care needs further investigation.

Elderly patients have been shown to have increased complications, prolonged hospital stay and higher readmission rates [74]. As expected, elderly patients, as a group, have more significant comorbidities, such as heart disease or renal dysfunction; it is therefore often difficult to manage supportive care issues. For example, with regards to antiemetic dosing in elderly patients undergoing chemotherapy, Gridelli has suggested that it is important to prescribe once-daily medications with low cardiotoxicity and low probability to evoke interactions with other drugs used in this population [75]. Gridelli cites the potential cardiotoxicity of the 5HT receptor blockers, and/or the potential drug interactions between the commonly prescribed antiemetics in the elderly population. The treatment of CINV in the elderly is only one consideration when looking at the impact of comorbidities on supportive care; however, one may imagine other potential complications; for example, the effect of uncontrolled hypertension and diabetes affecting kidney function in patients who are obstructed or scheduled to receive nephrotoxic chemotherapy. Overall, QoL will be enhanced with the tight control of medical comorbidities and, therefore, this plays a role in supportive care.

Complementary & alternative medicine

The use of complementary and alternative medicine (CAM) in gynecologic oncology patients is widespread [76]. Von Gruenigan *et al.* demonstrated that the use of CAM went

from roughly 25 to 50% over the course of 6 months after adjuvant therapy for ovarian cancer [77]. Women reported using CAM to cure and relieve symptoms affecting their QoL. It may be that the use of CAM correlates with an increase in supportive care needs that was not being addressed by providers. Swisher *et al.* report that the types of CAM are heterogeneous, and that patients in this population frequently use a combination of different remedies [76]. Approximately half of the 56 patients reported using some form of ingestible CAM, such as herbal preparations, diet, teas or vitamins. Interestingly, and unfortunately, only a minority of the women could give specifics as to the name and dosing of the CAM they were using. A larger proportion, 79%, of women reported using psychological or spiritual therapy, such as faith healing or meditation.

With respect to CAM, it is difficult to find studies demonstrating the actual effect of CAM usage on QoL. For example, in a study concerning exercise programs and their effect on QoL after chemotherapy, although exercise improved cardiorespiratory fitness, it failed to have a demonstrable effect on QoL measures [78]. It is interesting to note that in the endometrial cancer population (which is composed predominately of an obese group), it has been shown that patients prefer counseling regarding exercising and fitness to be provided in the setting of a cancer center [79]. Furthermore, these patients favored face-to-face counseling regarding their exercise program. These findings again stress that it is important to have oncologists, and/or their staff, participate actively in the supportive care of their patients, including enquiring about CAM usage, diet and exercise. Finally, both exercise and weight have been correlated with QoL scores, thus stressing the importance of considering these factors when addressing supportive needs [80].

Patients also expect physicians to address their psychosocial needs, even 24 months after completion of therapy [81]. It has been suggested that physicians be facilitators, and enquire about a patients psychosocial concerns, including spiritual concerns and advanced directives. Hodgkinson *et al.* found that it is these psychosocial needs that are mostly unmet in the supportive care realm [82]. As some patients may expect their oncologists to address these concerns, it may be worthwhile to add members to the gynecologic oncology team who specialize in these areas.

Expert commentary

In the review of the literature, two noteworthy conclusions can be made: first, patients are often reluctant to discuss supportive care issues; second, oncologists either lack novel ideas for the treatment of supportive care complaints, or they fail to be attentive to these issues, secondary to their focus on treatment of the cancer itself. In order to improve the care of women suffering from gynecologic cancers, one must clearly define the different components of supportive care, so that we

Key issues

- Supportive care issues are multifactorial, and can thus be intimidating for providers. Perhaps organization into two groups, treatment-related and tumor-related, provides a framework within which to manage these issues.
- Chemotherapy-induced nausea and vomiting greatly affect quality of life, and is a supportive care need that warrants special attention to well-organized treatment algorithms, which direct therapeutic choice.
- Cancer-related pain may be an under-reported symptom [79].
- There is a high incidence of depression and anxiety in gynecologic malignancy, and patients should be encouraged to actively seek support regarding how to increase quality of life. Sexual functioning may also benefit from psychosocial interventions.
- Fatigue is the most commonly reported symptom in gynecologic oncology patients, with anemia being perhaps the most frequent causative agent.
- The use of recombinant human erythropoietin, while helping patients to avoid transfusions, has a noteworthy risk of venous thromboembolism and future research needs to factor quality of life into the algorithm for treatment of anemia.
- Supportive care includes addressing the iatrogenically induced side effects of therapy, such as vaginal fibrosis, peripheral neuropathy and hypoestrogenism. Unfortunately, there is a lack of adequate data, as well as a consensus in the literature regarding optimal prevention and treatment of these effects, which may be particularly frustrating for the patient. However, hormone replacement therapy is useful in the management of menopausal symptoms.
- There are multiple burdensome and unavoidable effects of the tumor itself, such as lymphedema, ascites and dyspnea. Future clinical trials should investigate novel therapeutic choices which should include quality of life interventions.
- The supportive and medical management of bowel obstruction should be to decrease the intensity of pain, nausea, dry mouth, thirst, dyspnea, feeling of abdominal distention and drowsiness in the palliative setting.
- The psychosocial component of supportive care should include inquiring about a patient's use of CAM, and other unmet needs related to a patient's psychological health. Gynecologic oncologists may be involved in caring for patients who expect assistance in the search for spiritual care. When the need is not communicated, and/or not met, this might present a barrier in the patient–doctor relationship.

may be able to incorporate these needs into the primary anticancer treatment regimen in an organized manner. It would be ideal to integrate a questionnaire on supportive care for each patient's visit. This may allow for structured and regular reconciliation of supportive therapy. As these needs are met, the goal is for QoL to improve, and with the improvement in QoL we may expect to see improved survival outcomes in several gynecologic cancers [83,84].

Five-year view

With increased inclusion of QoL components in randomized clinical trials in gynecologic oncology [83,84], oncologists have come to recognize QoL scores as important prognostic tools. As we understand the importance of QoL, before and throughout therapy, gynecologic oncologists should enquire about QoL issues in their visits with the patient. Buried in these issues are supportive care needs. Hopefully, within the next few years, the gynecologic oncology literature will better define practice guidelines with respect to the topics discussed in the review. Perhaps more importantly, we can encourage our patients to discuss these needs, and to feel confident that their needs will be met. The impact of discussing these supportive care issue should improve QoL, as we have seen that the psychosocial component is perhaps the most critical. Prospective studies that include direct QoL interventions are needed.

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