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Comprehensive care in gynecologic oncology: The importance of palliative care

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HIGHLIGHTS

- Comprehensive care includes symptom management at diagnosis and extending through treatment.
- Management of complex symptoms associated gynecologic cancers with end of life care is reviewed.
- Communication and symptom management should be prioritized in gynecology oncology education.

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Introduction

Palliative care is a philosophy aimed at enhancing quality of life through the effective management of pain and distressing symptoms while incorporating psychosocial and spiritual care based upon each individual's values, beliefs and culture. Palliation incorporates efforts to relieve pain and suffering from diagnosis onward, facilitates effective communication between the patient and practitioner, and supports the goals of cure, life prolongation or acceptance of death.

The Society of Gynecologic Oncology is committed to promoting and ensuring the highest quality of comprehensive clinical care throughout the continuum of disease and therefore feels that incorporation of palliative care principles is crucial to the delivery of quality care to women diagnosed with a gynecologic malignancy. This is especially important as the early incorporation of palliative care principles into the management of oncology patients has been associated with clinical benefit [1]. A collaborative team approach is most effective in addressing the physical, psychosocial, and existential needs of patients, with support beginning for patients at time of initial diagnosis transitioning through

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effective management of treatment associated-toxicity, and ultimately for some moving to hospice at the end of life. In addition to the primary oncologist, this team may include a number of key participants including a primary care physician, case management, psychologists, spiritual counselors, and specialists in palliative care. This review focuses on the communication with and management of common symptoms for patients with advanced gynecologic malignancies.

Breaking bad news

As gynecologic oncologists, there are many times we are required to break bad news. This can occur in several settings, such as discussing unexpected surgical findings or a surgical complication, revealing test results indicating cancer progression, or informing patients of the implication of an inherited genetic trait. For patients, bad news that is communicated poorly can lead to increased levels of stress and anxiety, and in some series has been associated with poorer health outcomes [2]. Despite this, there is little training of either physicians or fellows as to how our patients perceive the delivery of and impact of such news. In a recent survey of fellows in gynecologic oncology, although 75% noted that they had cared for 11 or more dying patients, only 42% reported being explicitly taught to tell a patient she is dying [3]. We anticipate that this is a skill that is acquired during training, a skill that does not require specific instruction or refinement; however, a review of oncology studies has shown that structured education in palliative care can improve the comfort level of graduate medical trainees in breaking bad news [4]. Furthermore, although communication skills training has not necessarily been associated with improved health outcomes, it has resulted in improvement in communication as noted by patients.

Curricula have been developed in oncology to cover communication skills such as how to break bad news and discuss unanticipated adverse events. A recent literature review by Kissane et al. from MSKCC described a model for communication skills training for oncology fellows as well as methods for assessment [5]. Baile et al. from MDACC in 2000 described the "SPIKES method" (Table 1), a six-step protocol for developing bad news [6].

Table 1
SPIKES — a six-step protocol for delivering bad news (Baile et al. The Oncologist 2000, 5:302–311).

Step 1 S — SETTING Up the interview	• Arrange for privacy • Involve significant others • Sit down • Make connection with the patient • Manage time constraints and interruptions
Step 2 P — Assessing the Patient's PERCEPTION	"What is your understanding of your medical situation?"
Step 3 I — Obtaining the Patient's INVITATION	"How would you like for me to give the information about your test results?"
Step 4 K — Giving KNOWLEDGE and information to the patient	• Provide a warning shot = "I'm afraid I have bad news …" • Appropriate level of comprehension and vocabulary for patient • Avoid excessive bluntness • Give information in small chunks and reassess patient understanding
Step 5 E — Addressing the Patient's EMOTIONS with empathic response	Empathic response consists of 4 steps • Observe for emotion on part of patient • Identify emotion of patient • Identify reason for emotion • Let patient know you have connected with the emotion
Step 6 S — STRATEGY and SUMMARY	• Determine patient's specific goals/fears • Establish plans to address patient's goals/fears

It is also crucial that care providers are aware not only of how to communicate bad news, but also the certainty of the news delivered. Clinicians have been consistently found to overestimate survival in terminally ill cancer patients [7] which can affect the expectations and goals of both patients and their loved ones. A frank discussion of prognosis and the goals of cancer treatment can provide a basis for the effective management of symptoms in patients with advanced gynecologic malignancies. It can also provide an opportunity to review anticipated symptoms as well as the interventions available to relieve discomfort. The remaining sections of this paper will focus on common symptoms encountered in patients with terminal gynecologic malignancies and guidelines for best supportive care.

Dyspnea

Dyspnea characterizes the sensation of breathing discomfort and is one of the most common symptoms reported by terminal cancer patients. Dyspnea is very much a subjective symptom and can vary in both quality and intensity. Similar to pain, its presence and severity cannot be quantified by physical exam or laboratory testing, therefore, it is important to evaluate each patient individually and address possible underlying, and potentially reversible causes. Dyspnea can also have a significant impact on a patient's psychological well-being and is associated with anxiety and depression, particularly during acute episodes [8]. For many patients with terminal illness, the etiology of their dyspnea may not be treatable. However, in some cases, there may be specific treatments that provide symptom relief without compromising goals of less invasive therapies (Table 2).

There are a few effective supportive measures that can relieve or mitigate dyspnea. Relaxation or distraction techniques such as guided imagery, cognitive behavioral therapy, and music may be helpful in times of acute exacerbations. Facial cooling by using a fan to blow cool air over the face also helps diminish the perception of dyspnea. Chest wall percussive or vibration therapy can be useful for patients with difficulty mobilizing secretions. Finally, breathing techniques, such as pursed lip breathing and diaphragmatic breathing, as well as walking aids may also be helpful in controlling symptoms [9].

Supplemental oxygen is a standard treatment for patients with hypoxemia and appears to have some benefit in the management of dyspnea. However, it is important to note that the presence of hypoxemia does not predict symptomatic relief from supplemental oxygen therapy. Oxygen saturation does not always correlate with the subjective sensation of dyspnea. It is therefore reasonable to initiate supplemental oxygen in dyspneic patients with hypoxemia, but it is equally reasonable to discontinue its use if it does not provide effective symptom relief [10].

For patients in whom the above measures are inadequate, there are pharmacologic options. Systemic opioids are considered the most well established and first line agents for relief of dyspnea; of these, morphine is the most widely studied. Individual dose titration is important as drowsiness is a common side effect, as well as the potential for

Table 2
Dyspnea. etiology and intervention strategies.

Disease process	Possible intervention
Pneumonia	Antibiotics, pulmonary toilet
Lymphangitic tumor	Diuretics, glucocorticoids
Pneumonitis, radiation or chemotherapy induced	Glucocorticoids
Venous thromboembolism	Anticoagulation, IVC filter
Pleural effusion	Indwelling catheter, thoracentesis, VATS, pleurodesis
Airway obstruction by tumor or lymphadenopathy	Radiation therapy, glucocorticoids
Bronchoconstriction (COPD, asthma)	Bronchodilators, glucocorticoids
Retained or excess secretions	Anticholinergic agents
Massive ascites	Drainage, including indwelling catheter
Anxiety, including hyperventilation	Anxiolytics, cognitive behavioral therapy

respiratory depression. In a opioid-naïve patient, morphine at a dose 2.5–10 mg PO Q 4 h or 1–3 mg IV Q 1 h is an effective starting dose [11]. Nebulized opioids are an attractive option for providing treatment in hopes of limiting side effects, however, placebo controlled trials have not shown any benefit over placebo [12].

There are also several adjunct therapies that can be used in conjunction with systemic opioids for additional relief of dyspnea. Benzodiazepines, such as lorazepam (0.5–1 mg PO Q 4 h prn) are particularly useful in patients with anxiety related to their dyspnea [11]. Patients with COPD or a smoking history may benefit from bronchodilators. Finally, diuretics and/or glucocorticoids may help relieve dyspnea related to heart failure, lymphangitic carcinomatosis, or radiation and/or chemotherapy induced pneumonitis.

Pleural effusions

Pleural effusions are a common cause of dyspnea in patients with terminal cancer, particularly gynecologic malignancies such as ovarian cancer. Other symptoms related to pleural effusions include cough and chest pain. Initial management typically includes thoracentesis; this is useful in determining its effect on dyspnea as well as the rate of reaccumulation, although in the vast majority of patients the effusions recur within 30 days.

Repeated thoracentesis is not an ideal long term strategy as this involves repeated procedures and increases the risk of infection, adhesions, and loculations. Options include chemical pleurodesis or a long-term indwelling tunneled pleural catheter. Chemical pleurodesis is a procedure that uses chemical agents, most commonly talc or bleomycin, to cause inflammation, fibrin deposition, and resultant adhesion of the layers of the pleura to prevent fluid accumulation. Success rates range between 50–100%, and side effects include pain, atelectasis, pneumonitis, and acute respiratory failure due to systemic and pulmonary inflammation from the sclerosing agent. Candidates include those in whom the lung shows full re-expansion following thoracentesis [13].

Indwelling tunneled pleural catheters are another effective option and are often used in the gynecologic oncology patient. This device allows for repeated, intermittent drainage in an outpatient setting, thus increasing patient autonomy. Up to 1000 mL of fluid can be drained safely. Possible complications include catheter dislodgment, loculation, and infection. A recent randomized controlled trial was conducted to determine the efficacy of indwelling pleural catheters compared to chest tube insertion with talc pleurodesis in patients with malignant pleural effusion [14]. There were no significant differences in self-reported dyspnea in the two groups, but patients with indwelling catheters did experience more adverse events including pleural infection, cellulitis, and catheter blockage (40%) compared to chest tube with talc pleurodesis (13%).

Hemorrhage

Terminal hemorrhage in cancer patients occurs infrequently but management is difficult and based on expert opinion rather than research. There is no uniform definition of "terminal hemorrhage" but it is usually associated with rapid blood loss (internal or external), rapid volume depletion and often death. Reported incidence of significant bleeding in patients with advanced cancer is 6%–14% and terminal hemorrhage is 3%–12% [15].

Hemorrhage can be classified by its cause: 1) anatomic, related to tumor invasion or erosion of blood vessels due to neovascularization; 2) generalized, pathologic conditions associated with cancer or cancer treatment — thrombocytopenia, coagulopathy; and 3) mixed, combination of the two.

The most common sites of bleeding are gastrointestinal (GI), genitourinary (GU) and respiratory tract (RT). While bleeding from the GU tract is easily identifiable, the diagnosis of internal bleeding might be difficult and require time to diagnose with imaging. Volume resuscitation is an essential first step and a decision for blood transfusion needs to be made on an individual basis. Any existing hematologic deficiency or coagulopathy should be corrected as soon as possible. Specific interventions might be employed to control bleeding anatomically.

Moderate vaginal bleeding can be controlled initially with packing. External-beam radiotherapy may also be successful in controlling bleeding in patients with vaginal, vulvar, cervical and uterine cancer. Hypofractionation (for example, 2 fractions over 2–3 days) appears to be as effective and less distressing to patients than multiple fractions given over extended days in clinical cases associated with advanced pelvic malignancies [16]. Courses of hypofractionation can be completed with 2–4 week rest intervals between treatments up to a dose of 4440 cGy with no significant differences noted in response rates or complications. Transcutaneous arterial embolization, endoscopy, surgical ligation of large vessels, or excision of bleeding tissue are tools that may be helpful on case by case basis.

Invasion of tumor into the vasculature of lower GU tract is one of the most common causes of hematuria. Another common cause of hematuria is hemorrhagic cystitis related to exposure of urotoxins from chemotherapy, radiation and less frequently infection. About 20% of patients who receive pelvic radiation will experience bladder complications over their lifetime. As many as 14% of patients will experience grade 3 complications up to 20 years following treatment, frank bladder hemorrhage is rare and only occurs in 1% to 2.3% of patients and is dependent upon on radiation dose. Hematuria can be treated initially with bladder irrigation, and if not resolved, cystoscopic evaluation and coagulation is appropriate [17]. If hematuria is refractory to irrigation and cannot be coagulated during endoscopy, infusion of 1% alum is recommended. If alum therapy fails, administration of PGE2 and silver nitrate is the next step. Formalin can be used as a last resort and is reported to be 80% effective [18].

It is important to identify patients at risk for hemorrhage and prepare the patient, the family and medical team as this is an extremely distressing event for patients and their family members. It is crucial to discuss potential of hemorrhage in advance and to determine whether the patient is a candidate for an intervention. All measures should be taken to prepare for a potentially fatal event if hemorrhage occurs in a terminally ill patient. The following steps are recommended [19]:

- Ensure presence of a nurse or trained personnel,
- Provide psychological support to the patient and their family,
- Apply pressure if possible,
- Use dark towels and suction,
- Administer oxygen
- Consider sedatives or narcotics.

Midazolam, is a rapid-acting sedative and should be available for sedation in patients with terminal hemorrhage. Caregivers should be educated on administration of 2.5 or 5 mg given intravenously or subcutaneously and can be repeated as needed after 10–15 min.

Nausea and vomiting

Nausea and vomiting occur in 60% of terminally ill cancer patients. Nausea is stimulated from various receptors in the GI tract, chemoreceptor trigger zone (CTZ), vestibular apparatus, limbic system, and cerebral cortex. Vomiting is a neuromuscular reflex that results from this stimulation. Understanding the underlying mechanism of the nausea and vomiting can direct appropriate therapy [20]. Malignant bowel obstruction, a common cause of nausea and vomiting in ovarian cancer patients, is covered elsewhere in this review. Cerebral metastasis should be considered when other signs of meningeal irritation or emesis without nausea are present. Other causes include opioid use, impaired gut motility, metabolic abnormalities such as uremia, electrolyte imbalances, and hypercalcemia. In addition to targeting the underlying

Table 3
Characteristics of commonly used antiemetic drugs, adapted from "Handbook of Palliative Care in Cancer" Alexander Waller and Nancy Caroline, 1996 and Antiemesis. NCCN Clinical Practice Guidelines in Oncology Version 2.2014 (www.NCCN.org).

Class	Drug	Principal action	Route	Dose	Frequency	Major adverse events
Dopamine antagonist	Chlorpromazine	CTZ/vomiting center	PO/IM/IV	6.25 mg	Q8 h	Dystonia, akathisia, sedation, postural hypotension
	Prochlorperazine	CTZ	PO	50–10 mg	Q4–6 h	Dystonia, akathisia, sedation
			PR	25 mg		
			IM/IV	10–20 mg	Q3–6 h	
	Metoclopramide	CTZ/GI cholinergic	PO/IV	10–20 mg	Q2–4 h	Dystonia, akathisia, esophageal spasm, colic
	Haloperidol	CTZ	PO/IV	0.5–1 mg	Q8 h	Dystonia and akathisia, anticholinergic, sedation
Anticholinergic	Scopolamine	Vestibular, vomiting center	Trans-dermal	1.5 mg	Q3 days	Dry mouth, blurred vision, ileus, urinary retention, confusion
	Hydroxyzine	Periphery, GI tract	PO	6.25–25 mg	QHS	Dry mouth, sedation, dystonia
H_1 antihistamine	Diphenhydramine	Vomiting center	PO	50–75 mg	Q4–6 h	Sedation, dry mouth, urinary retention
			IV/IM	25–50 mg		
	Promethazine	Upper GI tract, vomiting center	PO/IM	12.5–25 mg	Q8 h	Dystonia, akathisia, sedation
5-HT3 antagonist	Ondansetron	Upper GI tract, ?CNS	PO/IV/SL	4–8 mg	Q4–8 h	Headache, fatigue, Constipation
	Dolasetron		PO	100 mg	Q 24 h	
	Granisetron		PO	2 mg PO	Q 24 h	
	Palonosetron		IV	0.01 mg/kg	1 mg Q 24 h	
			Transdermal	3.1 mg 24 h	Q 7 days	
			IV	0.25 mg	Q 24 h	
Steroids	Dexamethasone	Not known	PO/IV	4–24 mg	QAM	Hyperglycemia, headache, oral candidiasis, peptic ulcer, insomnia, anxiety, psychosis
Cannabinoids	Dronabinol	Vomiting center	PO	7.5–15 mg	Q3–4 h	Sedation, anticholinergic, euphoria, dysphoria, tachycardia
Benzodiazepine	Lorazepam	Not known	IV, PO	0.5–2 mg	Q4 h	Mild sedation, amnesia, confusion (avoid in elderly)

CTZ — chemoreceptor trigger zone; GI — gastrointestinal; CNS — central nervous system; PO — per os; IV — intravenous; IM — intramuscular; SL — sublingual; PR — per rectum.

mechanism(s), the following general principles should guide pharmacologic therapy: 1) use of optimal dosage and route; 2) around the clock dosing; and 3) addition of a secondary agent when monotherapy fails, rather than switching agents, to address multifactorial causes (Table 3). Careful attention to avoid combining agents with similar toxicities is necessary to reduce side effects. For example, prochlorperazine and haloperidol are both dopamine antagonists and when used together can increase the risk of dystonic reactions.

Anorexia

Anorexia is the second most common symptom in patients with advanced cancer and can be one of the most upsetting symptoms for caregivers. The complex pathophysiology of anorexia–cachexia involves inflammatory pathways and metabolic and hormonal changes. Anorexia is related to poor prognosis, lower chemotherapy response rates, decreased performance status, and decreased median survival [21]. Reversible causes of anorexia including constipation, pain, medications, hypercalcemia, and mucositis should be addressed. In advanced gynecologic malignancies, anorexia related to bowel obstruction may not be reversible. Examples of pharmacologic interventions include: 1) gastrokinetic agents such as metoclopramide that may be helpful in patients with nausea and early satiety; 2) low dose corticosteroids that are effective in improving appetite in the short term [22]; and 3) progesterone agents [23]. Cannabinoids, such as dronabinol have been studied and determined to reduce anorexia at the expense of toxicity with euphoria, hallucinations, psychosis and cardiovascular disorders. Because of the toxicity profile, cannabinoids are not a first choice of therapy [23]. In terminal phases, enteral feeding and parenteral nutrition do not reverse the metabolic derangements associated with cancer cachexia and anorexia and thus not recommended [24]. Educating patients and caregivers to focus away from nutritional goals during the end of life can alleviate the potential suffering associated with forced feeding.

Malignant ascites

Ovarian cancer has the highest incidence of malignant ascites compared to other cancers. Factors that contribute to the pathophysiology of malignant ascites include obstruction of lymphatic drainage, hepatic venous obstruction by tumor invasion into the liver parenchyma, and vascular permeability. Palliative strategies focus on removing ascites to relieve symptoms associated with distention including pain, dyspnea, early satiety, lower extremity swelling, and nausea. Paracentesis is the first choice for immediate relief of malignant ascites. PleurX drains have been shown to be safe and effective in refractory malignant ascites with 86% functioning until the patient's death [25]. Diuretic therapy may be effective for relief of ascites associated with portal hypertension from hepatic metastasis. Agents targeting the vascular endothelial growth factor (VEGF) have been shown to suppress ascites formation by affecting the microvascular tumor environment such as decreasing vessel permeability and interstitial fluid pressure [26,27]. Other novel strategies under investigation include intraperitoneal hyperthermic chemotherapy and immunologic therapies, but the costs and adverse events associated with these targeted agents and strategies may limit their use in this setting.

Malignant bowel obstruction

Malignant bowel obstruction is commonly seen in gynecologic malignancies, particularly in relapsed ovarian cancer patients. Approximately 35% of relapsed ovarian cancer patients are faced with a bowel obstruction, and complications of bowel obstruction are a common cause of death. Patients with a malignant bowel obstruction typically present with symptoms such as nausea, vomiting, abdominal pain/distention, constipation or liquid stools.

Conservative medical management with intravenous fluids, fasting (NPO), nasogastric tube, correction of any electrolyte abnormalities and adequate pain and nausea control is initiated at diagnosis and generally continued for period of time that ranges from 72 h to a week. If a patient then fails conservative management, three options are available, including surgery, chemotherapy or continued medical management. This is a highly individualized decision for patients and their physicians that depends on many factors, including extent of disease, likelihood of resectability of the site of obstruction, chance of response to further chemotherapy, overall estimate of life expectancy, other co-morbidities and patient preferences for their care [28]. There is no data to support the use of chemotherapy in alleviating malignant bowel obstruction; however, this only been examined in small case series [29–31].

The decision between surgery and continued medical management is challenging, with little evidence to guide management [32]. There is even less data on quality of life in ovarian cancer patients with malignant bowel obstruction managed surgically versus medically [33]. Surgery for malignant bowel obstruction is controversial, given the high mortality and morbidity and the low post-operative median survival. In a review of 700 surgeries for malignant bowel obstruction in ovarian cancer patients, the rate of major morbidity was 32%, and the median survival was 17 weeks [34]. In addition, 50% of patients either died or had a recurrence of symptoms within 90 days of surgery. Thus, surgery will not be the best option in the vast majority of patients. If surgery is to be performed, informed consent must address the high morbidity and mortality, the potential that the surgery may be unsuccessful, the long recovery with the possibility of ICU admission and the chance for re-obstruction. Although there is no available decision making tool for identifying patients who would benefit from surgery versus medical management, factors that have been associated with an unfavorable outcome include poor performance status, tumor free interval of <6 months, chemo-resistant disease, large volume ascites, multi-site disease, low albumin, multiple previous surgeries, prior radiation or intraperitoneal p32, palpable abdominal/pelvic masses, poor nutritional status and extreme weight loss [28].

Once the decision has been made for continued medical management in lieu of surgery, the nasogastric tube can be exchanged for a venting gastrotomy tube as a more long-term option. Venting gastrotomy tubes can be placed surgically, percutaneously with fluoroscopy or endoscopically. The morbidity and mortality of placement of a venting gastrotomy tube is minimal, and it can relieve nausea and vomiting in 90% of patients with restoration of some level of oral intake. In a select group of patients, flexible self-expanding metallic stents may also be used to bypass a reachable and localized area of obstruction. These stents are generally placed endoscopically or radiographically, and have a low risk of mortality and morbidity of placement. Lastly and most importantly, it is generally appropriate in patients who opt for continued medical management over surgery/chemotherapy for a malignant bowel obstruction to be referred for hospice care.

Patients and their families may ask about the use of TPN in the setting of a malignant bowel obstruction. Although this discussion can be difficult, they should be counseled that the addition of TPN is likely to add only 4–6 weeks of survival benefit with additional issues of cost, quality of life, and adverse events [30,31,35]. More recent data suggests that there may exist sub-groups of cachectic cancer patients, largely due to malignant bowel obstructions, that may benefit from TPN [36]. In a multi-center observational study with prospective follow-up of 414 cachectic cancer patients on home TPN, a combination of a low Glasgow Prognostic Score (GAS), a Karnofsky Performance Status (KPS) of <50 and the lack of metastatic tumor spread were associated with improved survival at 6 months (up to 43.7%) [36]. However, it is important to note that only 12.3% of patients enrolled in this study had ovarian cancer [36]; and thus, the generalizability of this data in gynecologic cancers remains unclear. As a general rule, TPN should be strongly discouraged in the management of malignant bowel obstruction resulting from recurrent or progressive disease. The only acceptable role for TPN in the management of a malignant bowel obstruction is to improve the nutritional status of the very rare patient deemed appropriate for surgery.

Other adjuvant agents that may be helpful in the medical management of malignant bowel obstruction include steroids and octreotide. Steroids are thought to decrease peri-tumoral edema and help relieve obstructive symptoms, and have the added benefit of their analgesic and anti-emetic properties. A trial of 4–5 days of dexamethasone is generally adequate to determine response. Concerns for the use of steroids in the setting of bowel obstruction include infection risk, aggravation of glycemic control, gastric ulceration and mood swings; and thus, should be rapidly tapered if there is no response to this treatment. Octreotide, an analogue of somatostatin, blocks the release of vasoactive intestinal polypeptide. This leads to a reduction in gastrointestinal secretions, motility and splanchnic flow which ultimately may decrease intestinal distention and colic. Octreotide has been evaluated in 15 randomized controlled trials and observational reports for a total of 281 patients surveyed, with a therapeutic success rate of 60–90% [37]. Unfortunately, cost can be prohibitory in its use.

Constipation

Constipation is a common complaint among gynecologic cancer patients in the palliative care setting, and can be disease-related or occur as a side effect of other drug therapies (i.e. opioids, serotonin antagonists, selective 5-HT3 antagonists, etc.). Bowel obstruction and fecal impaction should be ruled out before initiating therapy for constipation. Potential options for therapy include stool softeners (i.e. docusate sodium), osmotic agents (i.e. magnesium hydroxide, lactulose, PEG), stimulants (i.e. senna, bisacodyl), lubricants (i.e. glycerin suppositories) and enemas (i.e. mineral oil, soap suds). Bulking agents (i.e. dietary fiber, psyllium) tend not to be as helpful in this patient population, given that these women often have difficulty with adequate hydration.

It is estimated that 40–50% of patients on opioids will have opioid-induced constipation [38]. Thus, it is essential that a standing bowel regimen be prescribed with the use of scheduled opioids, usually consisting of docusate and senna to start. This bowel regimen can then be adjusted to ensure regular bowel movements, depending on what is "normal" for a particular patient. The opioid antagonist, methylnaltrexone, can be used for opioid-induced constipation in palliative care patients that are refractory to traditional laxative regimens.

Pain management

The symptom burden of pain in gynecologic oncology patients remains high. There is limited literature specific to gynecologic oncology outside of postoperative pain management. However, evidence-based guidelines addressing cancer pain also apply to gynecologic oncology patients.

When assessing pain, it is important to distinguish nociceptive pain from neuropathic pain. Nociceptive pain is frequently sharp, and precisely located. Neuropathic pain stems from dysfunction of the nervous system, and may be described as burning, tingling, or shooting.

The classic World Health Organization analgesic ladder set forth a model of increasing medications for increasing levels of pain (Fig. 1). More recently, the model has been revisited, such that non-opioids, adjuncts, education, and psychosocial support should be considered at each step along the way. Mild pain can be treated with non-opiate analgesics such as acetominophen, aspirin, or other non-steroidal anti-inflammatory drugs [39]. Acetominophen should be limited to no more than 4 g per day, and less (3 g) in older patients and those with liver disease. Aspirin may be limited by gastrointestinal side effects or allergy. NSAIDs increase the risk for gastrointestinal bleeding and nephrotoxicity.

Moderate pain can be treated with a combination of acetaminophen with an opiate, such as hydrocodone or oxycodone. A non-opiate alternative for moderate pain may include tramadol.

Treatment of severe pain begins with long acting opiate agonists such as morphine, hydromorphone, oxycodone, or methadone. Meperidine is generally not a good opiate for chronic pain in cancer patients because of its short half-life and metabolite which can cause seizures. Morphine, oxycodone, and fentanyl are all available in extended-release form as well as short-acting. A patient taking 60 mg of oral morphine daily is a good candidate to convert to using transdermal fentanyl, equivalent to a 25 μg patch every 72 h. Transdermal fentanyl may require 24–48 h to achieve pharmacologic steady state, so patients should continue using short-acting opiates while awaiting the full analgesic effect. Methadone is a particularly useful medication that is effective towards both nociceptive and neuropathic pain; it is inexpensive, with rapid onset of action, good oral bioavailability, and no known active

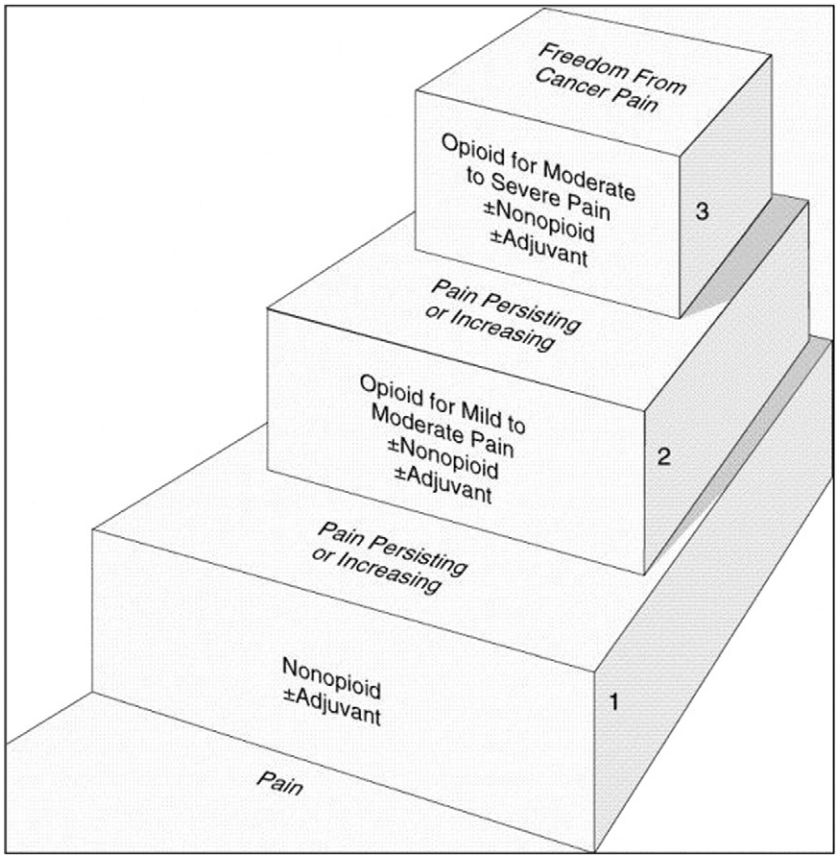

Fig. 1. The WHO analgesic ladder for cancer pain management: stepping up the quality of its evaluation. World Health Organization: Cancer Pain Relief. Geneva, Switzerland: World Health Organization, Office of Publications; 1986.

metabolites. There is some concern about methadone causing a prolonged QT interval [40].

Most pain can be fairly well managed with a combination of a long-acting opioid and a short-acting opioid for breakthrough pain [41]. Dosing of the long-acting opioid should be based on the 24 h needs. In general, the breakthrough dose should be 5–15% of the 24 hour opioid dose every 3–4 h [42]. Most long-acting opioids can be dose-adjusted every 2–4 days based on the prior days' need for breakthrough pain medication. There is no maximal allowable or effective dose for full opioid agonists; the dose should be increased to what is necessary to relieve pain with tolerance. Increasing pain medication needs is usually reflective of worsening of the underlying condition causing the pain. If rotating opioids, a less than fully equianalgesic dose is usually given to allow for incomplete cross-tolerance [42]. Note that a bowel regimen towards possible constipation should always be considered when prescribing opiate pain medications [38]. While most pain medications are administered orally, transbuccal, transdermal, and transrectal options are also available. Occasional patients require continued subcutaneous or intravenous medications. Adjunctive analgesics may be added to primary analgesics to improve pain control. These medications include anticonvulsants, antidepressants, muscle relaxants, and corticosteroids. Options for neuropathic pain may include tricyclic antidepressants, selective serotonin norepinephrine reuptake inhibitors, or gabapentin or pregabalin. A lidocaine patch may be helpful for localized neuropathic pain. Note that these medications may be helpful towards neuropathic pain, and are less likely to help symptoms of actual neuropathy, or numbness. Nonpharmacologic analgesic interventions such as ice, heat, massage [43], physical therapy, and acupuncture [44] can also be incorporated into pain management strategies.

Adjuvant meds and invasive procedures for pain

While analgesics are the backbone of cancer pain management, adjuvant medications, or co-analgesics, should be used to optimize pain control. Adjuvant medications are drugs whose initial indication was not for pain control, but have been found to be useful for this purpose, and can be used with analgesics on any step of the WHO analgesic ladder (Fig. 1).

The main indication for the use of co-analgesics is to increase the therapeutic index of opioids. However this is not to imply that adjuvants can be used with any less care than opioids. Adjuvants can actually be more difficult to manage, as most cannot be monitored via blood levels, are less flexible in terms of dosing and routes of administration, have a ceiling effect and can be associated with irreversible end organ damage. Khan et al. [45] compare and contrast analgesics in their 2011 article and salient features are presented in Table 4. There are five essential groups of co-analgesics: corticosteroids, antidepressants, anti-epileptics, NMDA-receptor channel blockers, and bisphosphonates (Table 5).

Corticosteroids

An estimated 40% of palliative care patients are taking steroids. While much of this use is for symptoms other than pain control, steroids have been reported to reduce pain [46,47]. However, no objective evidence supports this indication. Steroids reduce pain by decreasing inflammation and by limiting discharge from injured nerves. Low dose dexamethasone, 1 or 2 mg twice daily, is used for long term use and high doses, IV, 50–100 mg, are used for pain crisis. The side effects of steroids are well-described and quite common, therefore, the lowest

Table 4
Effects of opioids and adjuvants.

	Opioids	Adjuvant analgesics
Ceiling effect	No — titrate dose to balance analgesia and side effects	Yes, but with continued dose related toxicities
Therapeutic window	Wide	Narrow
Antidote	Naloxone	For some agents
Dosing	Multiple routes of administration, dose flexibility	Less versatile, less dose versatility
Regulatory issues	Many	Fewer, with exception of benzodiazepines
Onset of action	Can be immediate or sustained release	No role in the management of acute pain
Side effects	Seldom severe or life threatening	Specific to each class of drugs
Tolerance	Yes	No
Dependence	Yes	No, except benzodiazepines

effective dose for the shortest time period should be used, however, in the end stage setting, the long term effects may be irrelevant.

Antidepressants

Antidepressants are commonly used for neuropathic pain but can also be used as analgesics [48,49]. As analgesics, they are especially helpful with pain occurring in the setting of a depressed mood but can be effective independent of their effects on depression. Tricyclic antidepressants have been shown in systematic review to reduce pain at least moderately. Newer evidence also supports use of the serotonin norepinephrine reuptake inhibitors, specifically venlafaxine and duloxetine.

Anticonvulsants

The anticonvulsants gabapentin and pregabalin are FDA-approved for the treatment of some neuropathic pain [50]. These drugs have been shown to decrease cancer related neuropathic pain but not chemotherapy-induced neuropathic pain in randomized controlled trials. A trial comparing the two agents suggests that pregabalin is superior, though study design flaws call this conclusion into question.

NMDA-receptor channel blockers

Activation of the N-methyl-D-aspartate/glutamate (NMDA) receptor is associated with hyperalgesia, neuropathic pain and reduced functionality of opioid receptors, and blocking the NMDA receptor is associated with reversal of opioid tolerance. Ketamine, an NMDA receptor blocker, is an FDA-approved dissociative general anesthetic but can be used at much lower doses in the palliative care setting, usually for neuropathic pain [50]. There are no trials supporting the use of ketamine for cancer-related pain but there are reported case series. While the use of ketamine in this setting is gaining a following, a systematic review found insufficient evidence that ketamine improves opioids' treatment of cancer pain [51].

Invasive procedures for pain control

Some cancer patients will not be able to achieve pain relief with optimized use of opioids and adjuvants. Such patients may benefit from interventional therapies for pain management, usually nerve blocks, injections and implantable devices. These invasive procedures are performed and managed by specialists in this area, and while reports of success exist, there are limited objective data to support this approach.

Bone metastasis

Bony metastases are relatively uncommon in gynecologic cancers with literature reviews reporting rates of 1% or less in patients with endometrial and cervical cancers [52,53]. Despite the rarity, skeletal metastases cause significant clinical problems, including pain, pathologic fractures, hypercalcemia, and spinal cord compromise. Management of boney metastases should be aimed at reducing morbidity so that the patient's quality of life and functional independence are maintained. Treatment should be chosen based on the patient's clinical status, performance status, and disease status. Systemic control of the disease with chemotherapy should be considered, if appropriate, as this may be expected to help control bony symptoms.

For palliation of painful bone metastases, external beam radiation therapy is the most common treatment and is highly efficacious for patients with localized symptoms [54]. Treatment may be given in single or multiple fractions depending on the clinical situation. Pain control is also achieved by utilizing the classic, opioid-centered WHO analgesic ladder escalating to opioid use as needed. Adjuvant agents and nerve

Table 5
Commonly used adjuvants by class. Adjuvant Analgesics in Cancer Pain Management. D Lussier, AG Huskey, RK Portenoy. The Oncologist 2:571–591, 2004. NCCN guidelines in Adult cancer Pain management. Version 2.2014.

Class	Drug	Principal action	Route	Starting dose	Frequency	Major adverse events
Steroids	Dexamethasone	Inhibit prostaglandin synthesis	PO	1–2 mg	Q D or BID	Hyperglycemia Headache Oral candidiasis
	Prednisone	Decrease inflammation	PO	7.5–10 mg	Q D	Insomnia Anxiety Psychosis
Antidepressants	Desipramine	Tri-cyclic antidepressants (TCA)-inhibit norepinephrine reuptake	PO	10–25 mg	QHS	Prolong QTc interval Sexual dysfunction Anti-cholinergic effects
	Nortriptyline		PO	10–25 mg (may increase to 50–150 mg QHS)	QHS	Lower seizure threshold
	Venlafaxine	Serotonin-norepinephrine reuptake inhibitor (SNRI)	PO	37.5 mg (may increase up to 37.5–112.5 mg BID)	QD	Nausea Sexual dysfunction Somnolence Hypertension
	Duloxetine		PO	30 mg (may increase up to 60 mg)	Q D	
Anticonvulsants	Gabapentin	Inhibit depolarization of neurons	PO	100–300 mg (may increase up to 900–3600 mg in BID-TID doses)	QHS	Dizziness Somnolence
	Pregabalin		PO	50 mg (may increase to 100 mg TID)	TID	Mental cloudiness
Bisphosphonates	Pamidronate	Osteoclast inhibitors	IV	60 mg	Q month	Renal impairment
	Zoledronic acid		IV	4 mg	Q 21 days	Flu-like syndrome with initiation of treatment

blocks also assist in pain management for bone metastases as outlined previously.

Bisphosphonates, including pamidronate and zoledronic acid, are approved in the US and are helpful in management of both bone resorption and pain. Randomized clinical trials have demonstrated that bisphosphonates delay the onset and lower the incidence of bone metastases and their sequelae in patients with bone metastases from solid tumors by about 1/3. Bisphosphonates also reduce pain and improve quality of life [55]. Denosumab is a human monoclonal antibody that binds and neutralizes receptor activity of nuclear factor κB ligand (RANKL) thus protecting bone from degradation. Randomized clinical trials suggesting that denosumab is superior to zoledronic acid in breast cancer led to its approval for the prevention of skeletal related events in patients with solid tumor bone metastases in 2010 [56].

In some cases, surgery may be required to stabilize the skeleton. Metastatic disease to the vertebrae may result in spinal cord compression or instability. The use of vertebral body kyphoplasty may help manage pain associated with lytic vertebral body metastases in patients who are not surgical candidates [57]. Progressive neurologic deterioration is considered an emergency that requires immediate surgical intervention. Surgical decompression followed by postoperative radiation therapy may improve the likelihood of maintaining the ability to ambulate for patients with an expected survival of at least 3 months [58].

Hypercalcemia

Hypercalcemia, defined as total serum calcium above 10.2 adjusted for albumin concentration, occurs in up to 30% of patients with malignant disease [59]. Patients with hypercalcemia may be asymptomatic, but when symptoms are present, they are most commonly are gastrointestinal in nature, and may include nausea, vomiting, anorexia, and constipation. Polyuria may occur due to an impaired ability of the distal nephron to concentrate urine. Significant intravascular volume depletion results from a combination of these symptoms. Neurologic symptoms may begin with irritability and depression and progress to muscle weakness, delirium, and eventually coma.

Once hypercalcemia occurs, the cancer is usually advanced and anticipated survival poor (<6 months). Treatment for hypercalcemia should therefore be undertaken with consideration of the overall clinical situation. Intravascular volume expansion should be prescribed first. A reasonable treatment consists of a 1 liter bolus of normal saline, followed by an infusion of 75–150 cm^3/h. Bisphosphonates are the next step in symptomatic patients. Since the clinically apparent action of bisphosphonates is somewhat delayed, the most effective method for achieving a rapid and sustained reduction in serum calcium is to use a bisphosphonate in combination with calcitonin (2–8 IU/kg, SQ or IM Q 12 h). This should be reserved for patients with severe hypercalcemia, only. This combined use will lower serum calcium levels more rapidly than either drug alone.

Brain metastasis

The prevalence of brain metastases in patients with gynecologic malignancies is low. Detection of intracranial metastasis is often identified when patients present with symptoms that require intervention. Common presenting symptoms include headache (40–50%), seizures (10–20%), intractable nausea/emesis or neurologic symptoms such as hemiparesis, gait disturbance, and visual changes [60]. First line of therapy for brain metastasis is to institute steroids. This reduces cerebral edema surrounding the metastases and provides symptomatic relief within 24 to 72 h. Doses start at 4–8 mg/day of oral dexamethasone for patients with moderate to severe symptoms, which can be increased to 16 mg/day for severe symptoms. For patients with severe symptoms, you can exceed 16 mg/day and increase as much as 100 mg/day [61]. Patients with incidentally discovered brain metastases and no symptoms do not benefit from initiation of steroids [62]. If radiation is planned, steroids should be started 48 h prior to the start of treatment to counteract the possible worsening of cerebral edema and should be continued through the radiation course, and then tapered over at least 2 weeks following completion [62]. Anti-epileptic drugs (AED) are indicated only for patients who present with seizures as a manifestation of their metastases [63].

Multidisciplinary involvement with radiation oncology and neurosurgery is essential to provide best options for management in patients with brain metastases. While treatment options are based on a number of factors, the number of metastatic lesions is one of the basic triage points of NCCN guidelines for management [64]. For patients with 1–3 lesion and poor control of systemic disease, best supportive care or whole brain radiation (WBRT) is recommended [64]. For those patients with stable systemic disease or for whom good treatment options for their systemic disease remain, consultation with neurosurgery is recommended to determine if the lesions are resectable. For patients with 4 or more metastatic brain lesions or unresectable tumors, recommendations are for WBRT or stereotactic radiosurgery. WBRT is generally delivered in 10 fractions of 3 Gy or 15 fractions of 2.5 Gy (37.5 Gy) for patients with limited intracranial disease and good systemic options [64]. For patients with poor prognosis or performance status 5 fractions of 4 Gy may be used. The risk of developing radiation induced leukoencephalopathy and neurocognitive decline is present following WBRT if survival of >6 months is anticipated, so other options including WBRT with hippocampal sparing may be preferable.

Delirium

Delirium is highly prevalent in patients with advanced medical illness, occurring in up to 85% of patients at the end of life [65]. Delirium is characterized by an acute onset of disturbances in arousal, attention, and cognition that can wax and wane over time. These changes occur due to underlying medical problems associated with many adverse consequences including increased admissions or prolonged hospitalization, unnecessary medical interventions, increased mortality, and increased cost as well as significant distress for the patient, family and caregivers [66,67].

Delirium subtypes have been defined based on the presence or absence of psychomotor agitation and changes in level of consciousness. Hypoactive delirium is the most common subtype identified in a palliative care setting and is characterized by lethargy, sedation, and psychomotor retardation. It is generally associated with hypoxia, metabolic disturbances, or hepatic encephalopathy and has a higher risk of mortality than other subtypes of delirium [68]. Hypoactive delirium is also easily mistaken for depression. Hyperactive delirium is associated with agitation, restlessness, hyperactivity, hallucinations and delusions. It is often correlated with alcohol and/or drug withdrawal or adverse effects of medication [68]. Mixed delirium has alternating features of both hypo- and hyperactive delirium.

Delirium is often unrecognized and frequently goes untreated or inappropriately treated. It is important to note than even in the context of serious illness, physiologic disturbances that lead to delirium may be reversible, so diagnostic evaluation should include an assessment of potentially reversible causes. Common causes for patients with terminal gynecologic malignancies include: medications (benzodiazepines, opioids, steroids, anticholinergics), infections, fluid and electrolyte derangements, hypoxia, renal failure, liver failure, constipation and urinary retention [67]. However, in terminally ill patients, delirium is a reliable predictor of impending death [65]. As such, the clinician should take an approach in the evaluation and management of patients that is consistent with the goals of care. Goals for treatment of the dying patient may shift to providing comfort even at the expense of alertness.

Treatment of delirium should always be managed using nonpharmacologic interventions as well as pharmacologic strategies when indicated. Nonpharmacologic approaches include: providing familiar materials to help keep patient oriented, minimizing quantity of

stimulation the patient receives, use of family or volunteers as constant companions to reassure and reorient, minimizing use of restraints, and encouraging the use of glasses/hearing aids to promote communication [67]. For first-line treatment of potentially reversible, hyperactive delirium, evidence supports the use of antipsychotics such as haloperidol 0.5–2 mg every 2–12 h (PO, IV, IM, SC) or chlorpromazine 12.5–50 mg every 4–6 h (PO, IV, IM, SC, PR) to reduce agitation [66]. Atypical antipsychotics such as olanzapine and risperidone should also be considered as effective alternatives for patients that are intolerant of haloperidol. It is important to note that these agents are more expensive, have limited routes for administration (PO, IM) and have not been shown to have improved efficacy [67]. When irreversible, hyperactive delirium has been diagnosed, benzodiazepines such as lorazepam 1 mg SC or IM every 30 min may be most appropriate in place of, or in addition to haloperidol. Once the acute episode is controlled, the total dose of lorazepam used in the last 24 h should be determined and that dose divided into 2 doses given every 12 h. Hypoactive delirium is much more complex to manage and there is no clear consensus that pharmacologic interventions are beneficial [67].

The last 48 h of life

Approximately one-third of cancer patients will spend their final days in a hospital or intensive care unit [69], even though the quality of life is worse in this setting [70] and most patients with cancer prefer to die at home [71]. The reasons for this are complex and multifactorial, but failure to participate in hospice care is the variable most closely related to whether or not a cancer patient will die at home [72].

For those patients who spend their final days in the hospital, medical interventions in the last 48 h of life should focus entirely on comfort care. All non-supportive drugs agents should be discontinued as well any previously ordered laboratory tests and imaging. Drugs that need to be continued such as opioids, anxiolytics and antiemetics should be converted to the subcutaneous or intravenous route as patients will become weaker and may be unable to take oral medications at the end of life. Telemetry should be discontinued and patients with an implantable cardioverter defibrillator should have these devices deactivated in a situation in which palliation of symptoms is the goal as these may deliver painful shocks at the end of life leading to additional suffering [73]. Symptom control in the last 48 h of life most commonly includes pain, agitation associated with delirium, respiratory tract secretions and dyspnea.

Bronchial secretions or “death rattle” is a common symptom in dying patients caused by an accumulation of secretions in the airways. It is not believed to be painful for the patient, but treatment is often initiated because of distress of family members that are present at bedside. Repositioning the patient's head may reduce airway noise when weakening of the muscles in the head and neck results in increasing dysphagia and dangling vocal chords. Pharmacologic treatment of rattle includes glycopyrrolate (0.1–0.2 mg IV or SQ every 4 h), atropine (0.4 mg SQ every 15 min prn), or scopolamine (1.5 mg patch) [74]. Reducing additional fluids and feedings may also alleviate additional fluid accumulation in the body.

Conclusions

The Society of Gynecologic Oncology has been and continues to make efforts to promote education and research in palliative care. In addition to members seeking opportunities to develop their communication skills that enable them to discuss issues such as prognosis and unexpected results in a compassionate and straightforward manner, we believe that SGO should be at the forefront of developing both curricula for our trainees as well as continuing medical education for current gynecologic oncologists.

Conflict of interest

All conflict of interest forms have been submitted as requested. The authors have no conflicts of interest with regard to this manuscript.

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