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Evaluation of Prescribing Medications for Terminal Cancer Patients near Death: Essential or Futile

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Purpose
The purpose of this study is to evaluate the prescription of essential or futile medications for terminal cancer patients during their final admission.

Materials and Methods
We conducted a retrospective review of the medical charts of terminally ill cancer patients admitted to the Hemato-oncology Department of two teaching hospitals from March 1, 2007 to December 31, 2009. Essential medications were based on the drugs listed by the International Association for Hospice and Palliative Care, while futile medications were defined when short-term benefit to patients with respect to survival, quality of life, or symptom control was not anticipated.

Results
A total of 196 patients were included. Among essential medications, strong opioids were the most frequently prescribed drugs during the last admission (62.2% fentanyl, 44.3% morphine), followed by megestrol (46.0%), and metoclopramide (37.2%); 51% of gastric protectors were prescribed with potential futility. Anti-hypertensive and anti-glycemic agents were administered to those who experienced arterial blood pressure below 90 mm Hg (47.3%) or presented with a single measurement of fasting glucose below 50 mg/dL (10.7%), respectively. Statins were prescribed to 6.1% (12/196) of patients, and 75% of those prescriptions were regarded as futile.

Conclusion
Our data suggest that effective prescription of essential medications and withdrawal from futile medications should be actively reconciled for improvement of a patient's end-of-life care.

Key words
Drug therapy, Medical futility, Neoplasms, Symptom

Introduction

Medications are necessary for control of many symptoms in terminal cancer patients. In fact, patients with far-advanced cancer with short life-expectancies do not typically experience one symptom, but have multiple concurrent symptoms known as symptom clusters [1-3]. Because active anticancer modalities are limited to these patients, physicians should offer adequate necessary medications for maximum control in order to improve their quality of life. For example, such medications include opioids, which are recommended in the World Health Organization (WHO) publication on cancer pain relief options [4].

In 2007, the International Association for Hospice and Palliative Care (IAHPC) developed a list of essential medicines, based on efficacy and safety, for control of the most common symptoms experienced by patients receiving palliative care [5]. They identified 21 symptoms and included 33 essential medications for control of these symptoms. In

addition, according to a recent study based on international expert consensus opinion, four essential drugs were used for alleviation of anxiety, dyspnea, nausea and vomiting, pain, and respiratory tract secretions, as well as terminal restlessness [6]. These include morphine, midazolam, haloperidol, and an antimuscarinic, which should be offered in the last 48 hours of life for patients with cancer. The authors suggest that these four drugs should be available for alleviation of symptoms in all settings providing care for dying patients with cancer. Therefore, physicians who care for patients with far-advanced cancer should be familiar with these essential medications and be able to prescribe them beneficially.

Futile medication use in management of terminally ill cancer patients has also been reported [7,8]. However, identification of these medications for end-of-life care is challenging. Riechelmann et al. [7] defined a futile medication as unnecessary or duplicate. An unnecessary medication was described as follows; did not result in significant benefit to the patient in terms of symptom control or survival; had no scientific evidence for its use; had a goal of its therapeutic use was only expected to be reached after long-term chronic use. According to the results of that study, one-fifth of cancer patients at the end of their life took futile medications. In another study, medications to treat comorbid conditions were analyzed their futility as per explicit criteria [8]. In the latter study, it was observed that 21 out of 87 (24%) terminally ill cancer patients were taking futile or inappropriate drugs. These findings support routine performance of medication reconciliation for terminally ill patients.

To the best of our knowledge, simultaneous evaluation of essential vs. futile medication profiles of terminal cancer patients has not been previously performed; therefore, our aim was to examine the medications taken by terminal cancer patients during their final admission in order to explore patterns of medication usage.

Materials and Methods

We conducted a retrospective analysis of the medication profiles of terminally ill cancer patients admitted to the Hemato-oncology Department of two teaching hospitals located in urban areas of Korea from March 1, 2007 to December 31, 2009. Neither hospital operates a palliative care unit nor a palliative care team; each has an average of 35 oncology beds. We defined a terminally ill cancer patient as a patient who has progressed advanced cancer and a life expectancy of less than six months. Data on 196 terminally ill cancer patients who were admitted for management of terminal cancer and passed away in two hospitals were analyzed. We retrospectively analyzed medications on the patients' charts during two weeks of hospitalization before death. Patients still receiving anticancer treatment during the final admission and who had been intubated until death were excluded.

Data on the patients' demographics, diagnosis, cancer type, admission and death dates, comorbidities, and medications were gathered. Patients who had a hospital stay of more than one day were included. To examine the use of essential medications, the medication profile of each patient was evaluated for the 33 medications listed by the IAHPC.

We defined futile medication as stated above and performed an analysis for futile use. Self-administered drugs could not be analyzed, and therefore were not considered. Futile medications as unnecessary or duplicate were referred from the study reported by Riechelmann et al. [7]. Determination of futility of medications for treatment of comorbid disease was based on the study reported by Fede et al. [8]. In that study, the authors established criteria for classification of unnecessary medications: 1) gastric protectors (H1 blockers, proton pump inhibitors, antacids)—lack of any medical history of gastrointestinal (GI) bleeding, peptic ulcer, gastritis, or known chronic use (more than 30 days) of anti-inflammatory agents (steroids and nonsteroids); 2) anti-hypertensive agents—arterial blood pressure $<90\times60$ mm Hg at the time of the last consultation and symptoms of hypotension; 3) anti-diabetic agents—a single measurement of fasting glucose <50 mg/dL within four weeks of consultation or reported symptoms of hypoglycemia and a fasting glucose result below the normal limit; 4) statins—lack of any cardiovascular event in the previous 12 months.

Medical oncologists at the participating hospitals first performed medical chart reviews, and then the project staff reviewed the charts, resolving discrepancies by consensus of the researchers.

Statistics were used to describe the results. This study was approved by the ethics committees/institutional review boards of the individual hospitals.

Results

A list of the patients' characteristics is shown in Table 1. The median age of patients was 67 years, approximately half were male, and the most common primary tumor site was the GI tract (30.6%). The most common comorbid diseases were hypertension and cardiovascular disease (28.1%); others included diabetes mellitus (14.3%), hyperlipidemia (6.1%), cerebrovascular disease (5.1%), and hepatobiliary disease (2%).

Table 1. Characteristics of patients

Characteristic	No. (%) (n=196)
Median age (range, yr)	67 (27-101)
Gender	
Male	114 (58.2)
Female	82 (41.8)
Primary tumor sites	
Gastrointestinal	60 (30.6)
Lung	49 (25.0)
Hepatobiliary	28 (14.3)
Hematologic	22 (11.2)
Breast	9 (4.6)
Head and neck	8 (4.1)
Others	19 (9.7)
Comorbid disease	
Hypertension and cardiovascular disease	55 (28.1)
Diabetes mellitus	28 (14.3)
Hyperlipidemia	12 (6.1)
Cerebrovascular disease	10 (5.1)
Hepatobiliary disease	4 (2.0)
Median length of stay (day)	23.2

Medication profiles are shown in Tables 2 and 3. The most commonly prescribed drugs were opioids (fentanyl, 62.2%; morphine, 44.3%). In addition, morphine was administered for control of terminal dyspnea (23.4%). Megestrol ranked second (46.0%), followed by metoclopramide (37.2%). Medications for neuropsychiatric symptoms were prescribed for fewer than 10% of patients. Hyoscine butylbromide was rarely used (1.5%) for terminal respiratory congestion.

The potentially futile medications were classified as gastric protectors, anti-hypertensive agents, anti-diabetic agents, and statins (Table 3). Gastric protectors were used in 48.9% (96/196) of patients. Among 96 patients who took gastric protectors, 34.3% (33/96) of patients had reasonable co-morbid conditions, such as gastro-esophageal reflux disease, GI bleeding, and radiation esophagitis or ulcer. Steroid or non-steroidal anti-inflammatory drug together with gastric protectors was administered to 14.5% (14/96) of patients. The remaining 49 patients (51.0%) were prescribed without definite indication and these medications were provided until the patient's death by changing the administration route if the patient was unconscious. Total use for control of hypertension and diabetes was 28.1% (55/196) and 14.3% (28/196), respectively. Among those, anti-hypertensive agents were administered to 47.3% (26/55) of patients who experienced arterial blood pressure $<90\times60$ mm Hg, and anti-diabetic agents were prescribed to 10.7% (3/28) of patients who had a single measurement of fasting glucose <50 mg/dL. In addition, most of these medications were

Table 2. Prescribed essential medications listed on IAHPC classified according to symptoms

Medications (indication)[a]	No. (%)
Pain control	
Amitriptyline (neuropathic pain)	10 (5.1)
Carbamazepine	0 (0)
Codein (pain-mild to moderate)	0 (0)
Dexamethasone (neuropathic pain)	14 (7.1)
Diclofenac (pain-mild to moderate)	38 (19.3)
Fentanyl (pain-moderate to severe)	122 (62.2)
Gabapentin (neuropathic pain)	43 (21.9)
Hyoscine butylbromide (visceral pain)	12 (6.1)
Ibuprofen (pain-mild to moderate)	24 (12.2)
Morphine (pain-moderate to severe)	87 (44.3)
Oxycodone (pain-moderate to severe)	60 (30.6)
Paracetamol (pain-mild to moderate)	6 (3.0)
Tramodol (pain-mild to moderate)	61 (31.1)
Gastrointestinal symptom control	
Bisacodyl (constipation)	25 (12.7)
Codein (diarrhea)	0 (0)
Dexamethasone (anorexia)	0 (0)
Dexamethasone (nausea/vomiting)	7 (3.5)
Diphenhydramine (nausea/vomiting)	0 (0)
Haloperidol (nausea/vomiting)	7 (3.6)
Hyoscine butylbromide (nausea)	11 (5.6)
Loperamide (diarrhea)	9 (4.6)
Megestrol (anorexia)	90 (46.0)
Metoclopramide (nausea/vomiting)	73 (37.2)
Octreotide (diarrhea)	1 (0.5)
Octreotide (vomiting)	5 (2.5)
Prednisolone (anorexia)	4 (2.0)
Senna (constipation)	3 (1.3)
Neuropsychiatric symptom control	
Amitriptyline (depression)	2 (1.0)
Citalpram (depression)	2 (1.0)
Diazepam (anxiety)	16 (8.1)
Haoperidol (terminal restlessness)	9 (4.5)
Levomepromazine (delirum)	1 (0.5)
Levomepromazine (terminal restlessness)	
Lorazepam (anxiety/insomnia)	25 (12.7)
Midazolam (anxiety)	3 (1.5)
Midazolam (terminal restlessness)	6 (3.0)
Remeron	3 (1.5)
Trazodone (insomnia)	3 (1.5)
Zolpidem (insomnia)	7 (3.6)
Respiratory symptom control	
Morphine (dyspnea)	46 (23.4)
Hyoscine butylbromide (terminal respiratory congestion)	3 (1.5)

IAHPC, International Association for Hospice and Palliative Care. [a]Methadone was not counted because of its non-availability in Korea.

Table 3. Prescribed medications that have potential futility

Medication group	Futile use/Total use (%)
Gastric protectors	49/96 (51.0)
Anti-hypertensive agents	26/55 (47.3)
Anti-diabetic agents	3/28 (10.7)
Statins	9/12 (75.0)

continued until the patient's death. Statins were prescribed to 6.1% (12/196) of patients. We considered whether taking statins was primary prevention vs. secondary prevention according to the study reported by Bayliss et al. [9]. Taking statins for primary prevention is defined as hyperlipidemia only, while secondary prevention is for precancer diagnoses of coronary artery disease, history of stroke, peripheral vascular disease, and/or abdominal aortic aneurysm [9]. Statins for primary and secondary prevention were prescribed to 33.3% (4/12) and 66.7% (8/12) of patients, respectively. Among eight patients taking statins for secondary prevention, three patients had coronary artery disease or a stroke within the previous 12 months.

Discussion

Findings of this study demonstrated that opioids (fentanyl, morphine), megestrol, and metoclopramide were the most commonly used essential medications for terminal cancer patients during the final admission. We also found that some cancer patients took potentially futile medications; e.g., statins (4.6%) and multivitamins (3.0%), at the end of life. Futile prescriptions for gastric protectors, and anti-hypertensive and anti-diabetic agents were noted for 51.0%, 47.3%, and 10.7% of patients, respectively, according to the criteria defined by Fede et al. [8].

The symptoms experienced by cancer patients have varying impacts on quality of life (QOL). High levels of pain, depression, sleep disturbance, and fatigue were associated with a patient's worst functional status and poorest QOL [10]. The symptoms of hospitalized patients with advanced cancer have prognostic significance for prediction of survival [11]. A recent study highlighted the importance of symptom control by demonstrating symptom improvement according to the Edmonton Symptom Assessment Scale, associated with prognostic indicators for survival [12].

Frequently prescribed drug classes for cancer patients undergoing palliative care include analgesics, followed by laxatives and antiemetics [13,14]. According to a study on prescription use near death for patients with terminal illness, five medications (morphine, acetaminophen, dexamethasone, fentanyl, and metoclopramide) were the most commonly used for symptom control in the final months of a life-limiting illness [15]. Our findings are consistent with findings of that study. Analgesics, particularly strong opioids, were consistently prescribed to the greatest number of patients, followed by metoclopramide. Dexamethasone, for control of anorexia/nausea/vomiting, was prescribed less often; instead, megestrol was the most commonly used drug for control of anorexia. Drugs for control of psychological symptoms were rarely prescribed. Hyoscine, for control of terminal congestion, and haloperidol, for control of terminal restlessness, were also rarely administered (1.5% and 4.5%, respectively). These findings suggest a lack of assessment and treatment of these symptoms during the patients' final days. According to studies on changes in the clinical symptoms of terminally ill cancer patients before death, unclear consciousness (delirium, drowsiness) was the most common [16,17]. Death rattle showed a dramatic increase 48 hours before death [18]. Another study on use of midazolam for control of anxiety or breathlessness and haloperidol for confusion or agitation in cancer patients at the end of life reported that the overall frequency of sedative use tended to be low (22.6% and 24.8% at 48 hours and 24 hours before death, respectively). The authors of that study suggested more active use of sedative if indicated by demonstrating no deleterious influence on survival [19]. Because we could not perform an accurate search on medication use in correlation with symptom change as death approaches, the question of whether four essential drugs, morphine, midazolam, haloperidol, and an antimuscarinic, were prescribed for quality care of the dying was not properly evaluated [6]. However, despite consideration of this point, our data show definite lack of use of those drugs for patients enrolled in this study.

Which medications are futile for advanced cancer patients, especially those facing end of life? This is a difficult question, which requires consideration of various ethical aspects. The definition of medical futility is "an intervention that no longer provides benefit to patients, does not achieve a valuable goal, has a potential for harm and lacks benefits to justify resources" [20]. This may include unnecessary blood tests, radiologic examinations, and medications. We regarded futile medications as those that were used unnecessarily or were duplicated, as reported by Riechelmann et al. [7]. Futile use for control of comorbidities was referred from a study reported by Fede et al. [7,8]. The authors established criteria for unnecessary medications regarding gastric protectors, anti-hypertensive agents, and anti-diabetic agents. For example, gastric protectors were considered unnecessary in the case of a lack of any medical history of GI bleeding, peptic

ulcer, gastritis, or known chronic use of anti-inflammatory agents. Approximately 50% of our patients took gastric protectors until death. Due to the general lack of information about the patients' medical history, there was some difficulty in determining whether use of all gastric protectors was unnecessary. However, our findings highlight the need for awareness.

Anti-hypertensive agents and anti-diabetic agents could be considered unnecessary for patients with low blood pressure together with related symptoms and hypoglycemia. Because we were unable to reliably determine patients' symptoms retrospectively, we could not consider these medications as definitively futile. However, anti-hypertensive agents were administered to 47.3% of our patients with arterial blood pressure < 90 mm Hg, and anti-diabetic agents were administered to 10.7% of those with a single fasting glucose measurement < 50 mg/dL. Medication reconciliation is essential for quality care of terminally ill cancer patients, reflecting a patient's performance decline and cachexia.

According to the study reported by Riechelmann et al. [7], statins (56%), followed by multivitamins (30%), were the unnecessary medications prescribed most frequently to ambulatory patients with advanced cancer. We also found that statins were prescribed to 6.1% (12/196) of patients in our study. According to the classification of Bayliss et al. [9], use for primary and secondary prevention was prescribed in 33.3% and 66.6% of patients, respectively. Among eight patients taking statins for secondary prevention, five patients did not have any coronary artery disease, stroke, or peripheral vascular disease in the previous 12 months. The other three patients who took statins had experienced related events during the previous 12 months. However, two of them had simultaneous cerebral vascular accidents along with disseminated cancers when they were diagnosed. Despite an ethically challenging decision, when a patient's life expectancy is very limited, discontinuation of lipid-lowering agents is recommended; representative cases include lack of symptomatic acute coronary events and burden for oral administration [21].

Physicians should carefully determine the timely withdrawal of these agents, given a patient's clinical situation and treatment benefit. Several criteria have been proposed for use in guiding medication management at the end of life. These include an understanding of drug metabolism and of patient's prognoses, accurate estimate of benefits and harms of medications, clear treatment targets, adequate time to anticipated benefit, and consistency with overall goals of care. Even if discontinuation of medication is appropriate, many clinicians may be unwilling to discuss it, however, it is possible to use patient-centered approaches to decrease medication burden while at the same time reassuring patients of continued care and attention [9].

This study has several limitations. Selection bias was possible due to our small patient cohort. Essential medications were not reviewed concurrently with symptom assessment and medications for comorbidities (gastric protectors, anti-hypertensive agents, anti-diabetic agents, and statins) were not evaluated accordingly with regard to whether their use was definitely futile. Prompt immediate discontinuation of these routine medications may not be needed when patients are diagnosed with a life-limiting illness. However, we may need to contemplate what kinds of medications are necessary or futile for terminal cancer patients because we have a tendency to get used to the routinized adherence behavior. Conduct of further prospective studies will be needed in order to determine whether patients' self-reported symptoms and effective medication changes are considered.

Conclusion

Despite these limitations, the current study is significant, raising awareness of the most appropriate prescription of medications to advanced cancer patients facing end of life by analysis of essential and futile medications simultaneously. Findings of our study suggest that physicians should be familiar with essential medications in order to maximize symptom control and be able to withdraw potentially futile medications for improvement of a patient's end-of-life care.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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