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Integrating Complementary Medicine in Palliative Care: A Call for an Inter-Disciplinary Collaboration

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The interplay between complementary medicine and palliative care, both of which emphasize a patient-centered approach in order to improve quality of life-related concerns, is extremely important in the oncology setting. The integration of evidence-based complementary medicine therapies within conventional palliative care can expand the available treatment options, especially for chemotherapy-induced toxicities for which conventional medicine options are often limited. The integration of complementary medicine in palliative care may also provide an opportunity to address the bio-psycho-social-cultural-spiritual perspectives of care among those patients and caregivers for whom traditional medicine plays and important role in their health belief model. This integration should evolve as an inter-disciplinary process, as opposed to the intra-disciplinary approach which is being taken in most oncology settings. The inter-disciplinary approach recognizes the variance in approach to patient care, while facilitating a multi-disciplinary approach and enabling specialists from both domains to provide care based on their clinical expertise as well as their perceived health-belief models of care.

Over the past four decades a paradigm shift has been occurring, in which patient-centered care has become the focus of palliative medicine. Palliative care is taking place throughout the oncology setting, which recognizes the importance of addressing concerns related to the patient's quality of life (QOL), and not only outcomes related to survival or other disease-centered parameters. Palliative medicine provides therapeutic options which can reduce the level of suffering among patients and their caregivers, while addressing bio-physical, psychological, social and spiritual needs.[1] Improving QOL may, in turn, lead to a reduction in the use of medical services,[2] and may even impact outcomes such as survival rates among patients undergoing treatment.[3] In light of these findings, the American Society of Clinical Oncology guidelines recommend that "*combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden*".[4] The World Health Organization (WHO) has also addressed the importance of palliative care, and provides recommendations for the provision of these therapeutic options as part of standard care.[5] Yet despite the widespread recognition of the importance of palliative care in the oncology setting, the WHO guidelines are often not being implemented, either because palliative care therapies are not recommended as part of the treatment protocol or because they are not being integrated into standard medical practice.[6]

Complementary medicine (CM) includes a wide range of non-conventional therapies, such as traditional and systematic medical approaches; the use of herbal and non-herbal supplements; and diverse methods of mind-body-spiritual, nutritional-based and manual-movement therapies. CM use is widespread among patients with advanced cancer, with as many as 70% reporting this practice before, during and following active treatment.[7] Many patients using CM

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believe that these therapies can prolong survival, enhance QOL, reduce chemotherapy-induced toxicities, and increase levels of energy and function.[8-11] For many patients with advanced cancer QOL is severely impaired, and the treatment options provided for this indication by conventional medicine is often limited in its effectiveness.[12] As a result, many patients and their caregivers seek out "natural" remedies, frequently with the goal of curing their cancer, this despite the lack of any evidence as to their effectiveness and with a potential for adverse effects, including interactions with conventional oncology drugs.[13]

Integrative medicine is a concept of care which sees as its goal the integration of CM as part of standard conventional care. Integrative oncology seeks to supplement conventional supportive and palliative care, further enhancing patient QOL.[14] Integrative oncology services have become part of an increasing number of leading cancer centers, and are typically headed by integrative physicians (IPs). The IP is an MD with dual training in complementary medicine and supportive care, working in a multidisciplinary team which includes CM practitioners who are either physicians, nurses or other health care practitioners, as well as non-medical practitioners of CM.[15] Integrative oncology treatments are individualized and patient-tailored, while at the same time following the findings of evidence-based research regarding their effectiveness and safety. Much research has been conducted supporting both of these aspects of CM care, which include explanatory (randomized controlled trials) as well as pragmatic (non-controlled or observational) studies. This research has found a number of CM modalities to be effective and safe for a number of QOL-related concerns, such as the reduction of pain syndromes and improving mood with therapeutic massage[16]; reducing cancer-related fatigue, chemotherapy-induced nausea and vomiting (CINV), anxiety and dyspnea with acupuncture[17-19];and beneficial effects of herbal products such as ginseng for CRF and ginger for CINV.[20,21]

Integrative oncology emphasizes the importance and centrality of communication between the IP and the "circle of care" which includes the patients themselves and their caregivers, as well as the health care professionals responsible for their care (oncologist, nurse-oncologist, psycho-oncologist, family physician and others). Maintaining open and non-judgmental communication between these parties is essential in establishing an effective and safe environment for the patient-tailored intervention. Such a plan needs to correspond with the concerns of patients and their caregivers, as well as addressing their expectations and willingness to undergo new and often unfamiliar treatment modalities. In addition to being tailored to individual needs and expectations, the integrative treatment plan needs to consider the social-cultural-religious context of the patient's health belief model. This is especially true in regions such as the Middle East, where collective values often take precedence over those of the individual.

Despite the difference in their fundamental conceptual paradigms, integrative oncology and palliative medicine share an approach which emphasizes the bio-psycho-spiritual and patient-centered aspects of patient care. Both recognize the importance of the need for continuity of care, which begins from the moment the cancer is diagnosed, through active treatment and finally advanced cancer and end of life care. Both employ multi-disciplinary teams which include physicians, nurses, psycho-oncologists and other paramedical professionals in palliative care, and non-medical CM practitioners in integrative oncology. What, then, separates these two paradigms of care? How is the role of the IP different from that of the palliative care specialist? And finally, should the two domains exist separately in an inter-disciplinary framework, or should they co-exist within the same intra-disciplinary setting?

Both palliative medicine and integrative oncology need to choose between specializing in one domain or maintaining a more broad and general perspective. The specialist approach tends to focus on the specifics, analyzing medical challenges from a top-to-bottom perspective which is atomistic and reductionist. In contrast, the generalist approach contemplates a more horizontal and inter-disciplinary view. Interestingly, many IPs and palliative care specialists come from specialties with a more generalist orientation, such as family and internal medicine, geriatrics and others. Indeed, IPs and palliative care specialists share a more peripheral and holistic perspective when addressing QOL-related aspects of care. In addition to their conventional medical education, IPs chose to undergo additional CIM training which requires them to internalize medical philosophies which are not taught in medical schools and which often challenge conventional medicine concepts of care. Many IPs have also taken courses in CM treatments such as acupuncture, homeopathy, mind-body and other techniques, in order to better understand the tools available. As such, the IP should not be viewed merely as a CM practitioner with technical knowledge (e.g., acupuncture). Rather, IPs and their team of CM practitioners should be seen as providing a non-conventional understanding on the meaning of health *vs.* disease, as well as on the meaning of healing *vs.* medical management and treatment, especially for QOL-related concerns.

In order for an effective and true integrative process to take place, it is our belief that integrative oncology should take place in an inter-disciplinary model with palliative medicine care, and not one that is intra-disciplinary. We acknowledge the temptation to combine the two approaches. After all, an oncologist can become familiar with the use of herbal medicine; a psycho-oncologist can provide meditation and spiritual care; a palliative care specialist can insert acupuncture needles at designated points; and nurses can be trained in massage therapies such as reflexology. In practice, however, such a generalist approach is unlikely to succeed. The need for specialization in general fields of medicine is reflected in the establishment of subspecialty training in fields such as palliative medicine and psycho-oncology, and this should be the case for integrative medicine as well.

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Collaboration between IPs and palliative care specialists needs to be recognized for the many advantages which result from adopting an inter-disciplinary approach. This collaboration can be synergistic, with each discipline providing a solution for the other's "blind spots", significantly increasing the impact on QOL-related outcomes. The differences between these two paradigms of care are their strength, especially since both are committed to the same therapeutic goals. The IP consultation and CM treatments can supplement palliative care in cases where the conventional approach is not able to provide the necessary relief, as well as where there is an expectation regarding the patient's health belief model. Collaboration between IPs and palliative medicine specialists may reduce the "burnout" which results from work with palliative care, inducing a process of post-traumatic growth. And finally, palliative care specialists and IPs need to see each other as essential to patient care, enriching each other and advancing an inter-disciplinary collaboration within their joint medical institution.

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Editorial

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Distinguishing Between Cachexia, Sarcopenia and Protein Energy Wasting in End-Stage Renal Disease Patients on Dialysis

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Patients with end-stage renal disease (ESRD) receiving dialysis can have altered nutritional status and body composition due to dietary restrictions, level of physical activity, co-morbidities, metabolic alterations and inflammation.[1] As such, weight loss or wasting is common among this population with up to 75% of adults with ESRD undergoing maintenance dialysis displaying some evidence of wasting.[2] There are several forms of loss of lean muscle mass or wasting in ESRD, including 'protein energy wasting', 'cachexia', and 'age-related sarcopenia' and these terms are often used interchangeably alongside 'malnutrition' in current care. Limited understanding of the differences between such terms is arguably a barrier to accurate recognition and management of these disorders in patients with ESRD. For instance, a recent European study of over 700 dietetic participants concluded that only 13% of health care professionals who could differentiate between malnutrition, starvation, cachexia and sarcopenia.[3] Such knowledge is pertinent as for example, loss of muscle mass is a key feature in both sarcopenia and cachexia, but most patients with sarcopenia are not cachectic,[4] as muscle wasting occurs with aging.

Research has informed a disease specific definition (and associated diagnostic criteria) for protein energy wasting (PEW) in renal disease, and while cachexia in ESRD is seen as the severe form of PEW,[5] there remains no consensus definition or diagnostic criteria to differentiate between PEW and cachexia. What distinguishes PEW from cachexia is that the latter relates to only severe forms of metabolic depletion. However, PEW can refer to mild reduction of lean muscle and depletion of energy stores.[6] Alongside, the lack of disease specific definition or diagnostic criteria for cachexia, there is also no such disease specific criterion for sarcopenia in renal disease. The evidence-based development of these terms is essential to enable health care professionals to clearly identify and differentiate between such conditions. This greater understanding of the difference and interplay between cachexia, PEW and sarcopenia in ESRD

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has the potential to inform the development and testing of targeted novel therapeutic treatments aimed at reducing morbidity and mortality.[7] Significant progress has been made defining cachexia and its associated clinical characteristics in patients with cancer. An agreed definition and classification of cancer cachexia[8] has contributed to enhanced standardization of screening, staging assessment and management. This is a model that could be applied to cachexia in other chronic conditions, such as ESRD.

Reflecting the current evidence base, Table 1 outlines the characteristics of age-related sarcopenia, cachexia in chronic illness, and PEW in renal disease. These characteristics and associated pathologies are reviewed elsewhere in the literature,[5,9-11] and while the diagnostic criteria share similarities they are not identical. For example, weight loss is part of the definition of both cachexia in chronic illness and PEW in renal disease, but the duration of the weight loss differs (weight loss of 5% over 6 months in cachexia as opposed to 5% over 3 months in PEW). Additionally, the diagnostic criteria for cachexia in chronic illness emphasizes lean mass functionality (decreased muscle strength and fatigue), which is also common in sarcopenia of old age, although the defining characteristics of sarcopenia emphasize the importance of gait speed which cachexia does not. Furthermore, anaemia is considered a feature of cachexia in chronic illness, but not of PEW in renal disease or sarcopenia of old age.

	Sarcopenia of old age[9]	Cachexia in chronic illness[10]	Protein energy wasting in renal disease[5,11]
(i) Weight	Not stated, but weight gain is expected in obese sarcopenia whereas weight loss can occur otherwise	Oedema-free "unintentional" weight loss of at least 5% in 12 months or less in the presence of underlying illness. In cases where weight loss cannot be documented, a BMI<18.5 kg/m^2 or a drop from higher BMI to a BMI<20 kg/m^2 is sufficient.	Unintentional weight loss over time: 5% over 3 months or 10% over 6 months. Oedema-free BMI<23 kg/m^2 for example, post-dialysis dry weight.
(ii) Biochemistry	Not stated, but it is expected that serum creatinine relative to kidney function declines.	Increased inflammatory markers CRP (>3.0 mg/L), IL-6>3.0 pg/mL). Anaemia (<10 g/dL). Low serum albumin (<3.5 g/dl BGG or <3.2 BCP)	Serum albumin<3.8 g/dl (bromocresol green). Serum prealbumin (transthyretin)<30 mg/dL (for maintenance dialysis patients only; levels may vary according to GFR level for patients with CKD stages 2-5). Serum cholesterol<100 mg/dL
(iii) Muscle and/or fat mass	Low muscle mass<7.23-7.26 kg/m^2 for men and<5.5-5.67 kg/m^2 for women using appendicular lean tissue/height^2 by DEXA[12]	Low fat-free mass index. Lean tissue depletion i.e. mid upper arm muscle circumference<10th percentile for age and gender); appendicular skeletal muscle index by DEXA <5.45 kg/m^2 in females and<7.25 kg/m^2 in males.	Total body fat percentage<10%. Reduced mid-arm muscle circumference area - reduction >10% in relation to 50th percentile of reference population. Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months. Indirect measure of muscle mass, such as serum creatinine.
(iv) Muscle strength	Low muscle strength, handgrip strength<20 kg women and<30 kg men.	Decreased muscle strength (lowest tertile).	Not stated
(v) Functionality	Gait speed<0.8 metres per second.	Presence of fatigue - defined as physical and/or mental weariness, resulting from exertion; an inability to continue exercise at the same intensity with a resultant deterioration in performance.	Not stated
(vi) Dietary intake	Not stated, but often some decline in appetite and/or protein and energy is observed.	Anorexia. Limited food intake (i.e. total energy intake<20 kcal/kg /day; <70% of usual food intake) or poor appetite.	Unintentional low dietary protein intake<0.80 g/kg/day for at least 2 months for dialysis patients or<0.6 g/kg/day for patients with CKD stages 2-5. Unintentional low dietary energy intake<25 Kcal/kg/day for at least 2 months.
Diagnosis	Person must have column iii plus column iv or v.	Person must have column i plus three of the remaining five columns ii,iii,iv,v,or vi.	Person must have at least three out of the four columns i,ii,iii and vi and at least one test from each of the selected columns.

Table 1: Defining characteristics of sarcopenia of old age, cachexia in chronic illness and protein-energy wasting in renal disease.

As seen in Table 1, there are both variations and commonalities in the known clinical characteristics of sarcopenia, cachexia and PEW in a renal population. This may be reflective of the poly-symptomatic nature of ESRD. However, it makes the diagnosis of any of the three conditions more complex. Effectively distinguishing between these three conditions in ESRD is important, acknowledging that elements of sarcopenia and PEW may be present in cachexia, as interventional strategies may be very different for each. Work on delineating key clinical characteristics of PEW in renal disease has progressed extensively[13] and cachexia is viewed as a severe form of PEW.[5] However, the diagnostic criteria for cachexia in ESRD, as opposed to PEW, have not been agreed. This is significant as cachexia may involve additional metabolic abnormalities that are potentially amenable to therapeutic intervention.

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What should the next steps be? Adoption of a disease-specific definition of cachexia in ESRD would contribute to standardization of screening, assessment and management strategies that are aimed at improving morbidity and mortality in these patients. Such a definition needs to be derived in such a way to distinguish cachexia from both sarcopenia and PEW, should define a population group with a different prognosis from PEW, and needs to reflect our understanding of the pathophysiology (particularly the role of inflammation) of cachexia in other conditions such as cancer, heart failure and COPD. Such a definition would greatly facilitate screening, diagnosis and development of treatments for this life-limiting complication of end stage renal disease.[14,15]

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Opinion

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Transforming End-of-Life Care

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Currently, hospice care which focuses on caring for a terminally ill person delivers holistic, supportive, interdisciplinary, and patient-centered management. There have been numerous efforts to establish hospice care for people who are in the end-stage of their illness.

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (WHO). Hospice care which is a subset of palliative care focuses on controlling pain and other symptoms of illness so patients can remain as comfortable as possible near the end of life. The meaning of hospice care throughout this study is a supportive care to people in the final phase of a terminal illness and focus on comfort and quality of life.

Hospice care for people with end-stage illnesses, which can involve complex end-of-life care in a wide variety of settings, including bio-psycho-social symptom management, care related to cultural and ethical issues, bereavement care, and after-death care. Hospice care affects the end of life experience tremendously.[1] However, let us consider hospice care at this time. Does hospice care really deliver the right care for people in the endstage of their lives? What level of hospice care do most hospice patients receive? How many people can be supported with hospice care by the government for a dignified death? For how long is hospice care required for an appropriate or good death? How much respect is there for the human rights of people in hospice care?

Human dignity and human rights in end-of-life care are very important in terms of a person's identity and values, and they are accorded to and respected in everyone using hospice care services.[2-5] It is the responsibility of every hospice professional to know how to provide high quality care to people with end-stage illnesses in view of their human dignity.[5-7]

This paper provides an overview of transforming end-of-life care. It describes not only the highest quality care for people who have had a life-limiting illness but also the trends of preparation for death, respect for the free will of people, receiving professional hospice care, and quality care after death.

The goal of this paper is to contribute to the development of future hospice care from the perspective of the dignity of people. Much needs to be improved in areas such as hospice philosophy and practical support for transforming end-of-life care.

HIGHEST QUALITY CARE

The highest quality care in Hospice refers to the quality, compassionate care of people facing life-limiting illnesses. Compassionate care is also holistic care. People facing life-limiting illnesses need compassionate access to a more systematic way to meet their holistic needs. Compassionate care becomes a strong and powerful interaction that encourages the patient to participate.

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The approach of compassionate care takes into account the physical, emotional, and spiritual needs of each person. The method of delivering compassionate patient care is a ready-to-go solution to a very real problem, which involves supporting the patients and helping to meet their needs.[8-11]

The hospice care profession also provides spiritual and emotional support to hospice patients. Hospice providers encourage individuals to discover meaning and purpose as peacemakers. They provide support during difficult decisions while respecting individual beliefs. Spiritual care may or may not include religious care.

PREPARING FOR DEATH

Preparing for death is one of the most empowering actions. As people approach the end of their lives, they commonly face many decisions that range from simple to extremely complex. Dying persons and their families are faced with choices about what they want or need. These people can be prepared for death when they know their exact situation in detail.

These decisions may be physical, psychosocial, spiritual, or legal in nature. Each decision should ideally be considered in terms of relief of suffering and the values and beliefs of the dying individual and his or her family.[12-14]

At the moment, when people die, they leave their physical bodies behind. They pass through a dark tunnel to a transcendent spiritual existence. After they die, their family and friends remain. The emotional-spiritual-mental function involves a different kind of process.[14] The spirit of the person in the final process may need resolution of unfinished issues and relationships with life. The spirit completes its natural process of reconciling and finishing in a way that is appropriate and unique to the values, beliefs, and lifestyle of the dying person. Some may want to reflect on the meaning of life, some may decide to conduct a final life review or deal with psychologically unfinished business, and some may want to participate in planning rituals before or after death. The most appropriate responses to the emotional-spiritual-mental changes are support and encouragement about the resolution and the transition.

Waldrop and Meeker[15] identified five decisions that people make before the end of their lives: (1) operationalizing advance care planning, which is a renewed focus on decisions about care at the end of life; (2) surrogate decision making, in which caregivers begin making both informal and formal decisions for the dying person; (3) meaning-making, in which the foreshortened time brings into focus decisions about seeing special people, attending events, and creating memories; (4) location of death, which involves decisions about whether the person wants to, and can remain, at home to die; and (5) final acts, in which decisions about funeral arrangements, wills, and leaving a legacy become central.

Gauthier[14] mentioned that terminally ill adults make decisions based on a broad set of factors that influence how one responds to everyday challenges. In his study of decision making near the end of life, he also reported that open and honest communication about sudden functional changes in the context of chronic illness might allow individuals to choose hospice or palliative care earlier in the trajectory of their illnesses. Therefore, a hospice care team prepares the dying person to respond in ways that will help him or herto accomplish this transition. These teams also support and understand the responses of people in the final stage.

Preparing for death is a great gift of love as this moment approaches. The person is ready for this release emotionally, spiritually, and mentally because others will continue to live until the shutdown process ceases. All end-of-life choices and decisions have a significant impact on suffering, quality of life, and dying. People in this context may make choices about how to spend their limited time and energy. The time of preparing for death is a time to give full acceptance, support, and comfort. People also frequently make legal decisions about wills, advanced directives, and durable powers of attorney at this time.

The person approaching the dying process keeps in his or her mind the unresolved or un-reconciled important issues or some significant relationships even as all of their physical systems cease to function. Preparing for death needs to happen in a way that is appropriate and unique to the values, beliefs, and lifestyle of the dying person. It is closely interrelated with his or her physical, psychosocial, spiritual, and economic situation. Therefore, well-intentioned care by health care providers may overlook a particular person's wish not to discuss death.

RESPECT FOR FREE WILL

Free will is a freedom of choice and self-determination without external restraint when there is a choice of possible actions. Respect for the free will of people who are in the last days, weeks, and months of life requires hospice health professionals to understand the extent to which their preferences are being met. Respect for the free will of people who are in their last daysmeans improving the understanding of their needs and wishes by capturing their preferences and sharing the information when caring for the dying people. For example, a hospice health care team should consider how and where people hope to die and what they are concerned about. Each team should consider which type of care makes the most sense for each person. Hospice care in general can take place in different settings, including hospitals, outpatient palliative care clinics, nursing homes, certain other specialized clinics, and the home. The Patient Self-Determination Act (PSDA) of 1990 was developed to ensure that these rights were protected, including the fundamental rights to treatment choices, informed consent, truth-telling and open communication with health care providers, and control over the individual's own life and death. The core values of hospice care emphasize autonomy and individual rights to make life choices, especially

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health care choices. The health care provider in a hospice must have a clear understanding and recognition of the patient's desire. It is important to remember that people are aware of their own values, hopes, and beliefs.

PROFESSIONAL CARE

The professional care of people who are dying is mandatory for all hospice health professionals involved in end-of-life care, which includes skills for communicating with and supporting families and their advocates.[16,17] The hospice care providers include hospice nurses, doctors, social workers, physical, speech, occupational, or dietary therapists, home health aides, spiritual counselors, and volunteers as well as someone who is available as the primary caregiver at home. This person may be a spouse, partner, or other relative, such as a son or daughter, or even a neighbor or a team of people from the community.

Hospice care is most affected by the differences of the social and cultural recognition and the policy of the countries. So, professional hospice care should be made by considering the cultural aspects.

Professional hospice care is intended to help people who should be respected during every moment of their final days. Hospice professionals should help them using their professional knowledge and experience because they support the final-stage patients who have special psycho-socio-spiritual problems.[18,19] Hospice care providers serve not only to reduce physical suffering but also to help patients and their families spend meaningful time together. Hospice care professionals have helped patients and families to hold a family meeting to reassure the patient that everyone is ready to let go. Therefore, the members of hospice care teams want to know what to expect and how to respond in ways that will help the people who are in transition with support, understanding, and ease. Also, Chochinov[3] proposed a model dignity and dignity-converting intervention for patients serving nearing death by therapeutic conversation. Through dignity therapy, patients will be able to reduce psychological, spiritual and existential distress and to send the end of life with dignity.

QUALITY CARE AFTER DEATH

Human dignity is that all humans should be treated with respect regardless of sex, race, gender, class, nationality, religion, or other divisions. The dignity of the deceased is not overemphasized because he or she had an individual experience.[15,21] A dignified death means not only the alleviation of bodily suffering and pain but also the meaningfulness of death. The quality of care after death largely depends on whether staff members have received training in the care of dying patients.[22] Quality care after death reflects the importance of caring for the deceased body and the family because they have had their own individual experiences.

Quality care after death reflects the importance of caring for the deceased body and the family because they have had their own individual experiences. The dignity of the deceased is not overemphasized because he or she had an individual experience.[15,20] A dignified death means not only the alleviation of bodily suffering and pain but also the meaningfulness of death. The quality of care after death largely depends on whether staff members have received training in taking care of dying patients.[21]

End-of-life care calls on the skills of many different professionals and individuals to meet the patient's many requirements. Crucially, there is only one opportunity to ensure good care after death, and it is not easy to coordinate everything that needs to happen. Guidance, therefore, is a good practice, as is confirming a process by which everyone who is involved can ensure that the experience for those coping with the loss of someone important to them is as good as it can be. This whole process should be set within the context of the deceased's wishes about care arrangements, and family members should be given information and support. Stuart et al[22] identified after-death care as care/counseling of the family, religious/cultural requirements, staff availability, and the presence of funeral directors and pastoral caregivers.

CONCLUSIONS AND RECOMMENDATIONS

The goals of this paper were to explain the transformation of end-of-life care with a foundation of dignity for palliative patients and to develop a conceptual framework for the future perspectives of people approaching death. The quality end-of-life care in future should involve the highest quality care, preparation for death, respect for free will, professional hospice care, and quality care after death with a view to human dignity (Figure 1).

Figure 1: Transforming end-of-llife care.

It is complex and challenging, but the principal aim is to support people to die well in their preferred death. Good end-of-life care aims to treat people with dignity and respect in care. Some people who are able to access hospice and special pallia-

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tive care in communities or hospitals receive high standards of care in their final weeks, days, and hours, but many others do not. Despite the higher quality of end-of-life care and increasingly high-level qualitative data to support this, there is still a significant fragmentation of services and widely variable quality of care. A goal should be set for hospice and end-of-life care involving quality of care to increase annually.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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PALLIATIVE MEDICINE AND HOSPICE CARE

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Mini Review

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Morphine Mouthwash in Oral Mucositis: A Mini Review

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ABSTRACT

Oral mucositis is a frequent adverse effect of chemotherapy and radiation therapy in cancer patients. The mucositis impacts overall quality of life (QoL) by producing pain with variable intensity leading to difficulty in oral intake, lack of sleep, etc. A multimodal therapy is advocated for management of oral mucositis in cancer patients and includes certain preventive and therapeutic interventions aiming at symptom control. The systemic analgesics are frequently used but may be associated various side effects associated with analgesics including opioid. The use of oral submucosal route for opioids has been advocated in view of existence of peripheral opioid receptors for its analgesic property. We review the literature for use of morphine mouthwash for management of painful oral mucosisits.

KEYWORDS: Morphine; Mouthwash; Adverse effects; Mucositis; Cancer.

Cancer patients require multidisciplinary approach including chemotherapy and radiation therapy. Apart from other therapy associated side effects, oral mucositis remains a major concern for patient undergoing chemotherapy and/or radiation therapy.[1,2] The incidence of mucositis ranges 15-90%.[1-4] The oral mucositis is associated with chemo-radiation of head and neck cancer primarily. The usual chemotherapeutic drug regimen for patients with unresectable, locally advanced cancer is combination of cisplatin and 5-fluorouracil (5-FU) with concurrent radiation.[5-8] The 5-FU-based chemotherapies have more risk of mucositis.[9-11] The mucositis occurrence and its severity remain dose dependent (chemotherapeutic drugs, cumulative radiation exposure).[8,11] Continuous infusion of chemotherapeutic drugs leads to increased risk of developing mucositis.[8,12,13] The cancer patients receiving such combination of chemotherapeutic drugs along with radiation therapy remains at risk of painful mucositis which may result in interruptions of subsequent treatment. Thus, such symptom may not only adversely affect quality of life (QoL) but also affect the disease outcome.

The treatment related oral mucositis remains painful with variable intensity and at times severe pain leading to patient distress. It may affect overall QoL with decrease oral intake, painful deglutition, affect sleep and may result in serious clinical complications.[4,9,11] So such painful oral mucositis requires immediate intervention with various analgesics including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. However, use of NSAIDs requires caution in view of chemotherapy induced hematopoeitc suppression and also may not be adequate for control of moderate to severe pain.[1] Thus, need of opioid analgesics is frequently required based on severity of pain of oral mucosisits.[1,2] During the acute mucositis, oral intake remains painful and thus necessitating the intravenous administration of narcotic analgesics. Opioid administration is associated with various side effects commonly include sedation, dizziness, nausea, vomiting, constipation, respiratory depression, physical dependence and tolerance.[1,3] Therefore, effective use of systemic opioid requires balancing between pain relief and the undesirable side effects. The use of other adjuvant therapy may help in reducing the opioid requirement for optimal pain relief.

The use of topical anesthetics along with oral hygiene is useful for symptom management of painful oral mucositis.[14] Though the robust evidence do not exists, but mucosal coating

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agents with analgesic properties have been reported to be effective for management of painful oral mucositis. The opioid analgesics like morphine produces its analgesics effects by binding to opioid receptors in the central nervous system (CNS) and the peripheral terminals of afferent nerves.[15-17] The literature reports *via* various basic and clinical research about the analgesic efficacy of local application of exogenous opioid for management of painful inflammatory conditions.[18-21] The oral and parenteral analgesic effect of opioid are well established with robust evidence, but no unified approach with concrete evidence exists for topical treatments.[3,9,22] It has been shown that the opioid receptors exists in peripheral sensory neurons and thus can be activated by topical analgesics resulting pain relief.[23] It has also been reported that oral epithelial cells contain opioid receptors.[24] The opioid ligands with a preference for μ-receptors are generally most potent when applied locally.[15] Morphine has a predictable low absorption through the trans-mucosal route. The sublingual as well as trans-mucosal absorptions of drugs are dependent on both pH level and lipid solubility.[25,26] Therefore, morphine being less lipophilic (partition coefficient 0.00001) and ionized at the low pH level of the oral cavity (morphine pKa at 37 °C=7.9) is poorly absorbed.[27,28] Evidence of the activation of opioid receptors due to inflammatory change in tissues has led to the exploration of the potential analgesic effect of opioid peripherally.[29,30] This suggest that morphine mouthwash would provide optimal analgesia without getting absorbed systemically and thus less adverse effects. The literature supports the effectiveness of morphine mouthwash for treatment of oral mucositis in cancer patients (Table 1). The overall literature suggests that morphine mouthwash (1-2%) provide effective pain relief for 30-120 min-

Study	Intervention	Study design	Results	Adverse effects	Remarks
Mostafa et al[31]	30 patients with oral mucositis Grade 3 or 4 received morphine sulfate 2% or magic solution (magnesium aluminum hydroxide, viscous lidocaine, and diphenhydramine), 10 ml for every 3 h, six times a day, for 6 days.	Prospective randomized study	At the 6th day, more reduction was observed in mucositis severity in the morphine compared with magic group (p=0.045). Patients in the morphine group were more satisfied by their treatments than those in the magic group (p=0.008).	Nil reported	Topical morphine is more effective and more satisfactory to patients than the magic mouthwash in reducing severity of oral mucositis.
Vayne-Bossert P et al[32]	9 patients with oral mucositis of at least grade II received 15 ml of 2% morphine mouthwash or placebo, 6 times a day, for 4-6 days.	Randomized double-blinded crossover study	Pain alleviation 1 hour after mouthwash was significantly influenced by the gesture of the mouthwash (p<0.001) with either morphine or placebo) and almost by the efficiency of morphine (p=0.020). Duration of pain relief was 123.7±98.2 min with morphine.	Burning sensation by topical morphine caused one patient to drop out from the study	Authors suggest a possible analgesic effect of topical morphine.
Cerchietti et al[33]	26 patients were randomly assigned to morphine mouthwash (MO group=14 patients) or magic mouthwash (MG group=12 patients)	Randomize, controlled, parallel comparative study	Duration of severe pain was 3.5 days less in the MO group compared with the MG group (p= 0.032). Intensity of oral pain was also lower in the MO group compared with the MG group (p=0.038). More patients in the MG group needed supplementary (oral or parenteral) analgesia compared with the MO group (p=0.019). There was a significant difference in duration of severe functional impairment (p=0.017).	MG group reported nausea (1), loss of taste (3), viscous saliva (2), dry mouth (2) and excessive anesthesia (1) MO group reported dry mouth and a burning sensation in 1 patient.	MO is a simple and effective treatment to decrease the severity and duration of pain and the duration of functional impairment
Saroja S et al[34]	10 patients rinsed with 5 mg morphine sulphate in 15 ml of diluent solution every 2 hour and instructed to keep it in mouth for 5 min and then spit it out.	Open label study	Good pain relief lasting for 30-60 min.	Patients reported difficult rinsing initially because of the restricted movement of mouth opening due to trismus.	Oral morphine rinse resulted in effective of pain relief and improved opening of mouth in cancer patients with mucositis.
Nielsen BN et al[35]	12 children received oral morphine as atomizer oral spray. The morphine spray was retained in mouth for 10 seconds before spitting.	Prospective observational sequential study.	Pain decreased by 36% after 30 min of topicalization. The serum morphine and its metabolites levels were well below the effective analgesics levels.	None reported	Oral morphine topicalization provides effective pain relief.
Leamdro CA et al[36]	Conducted in two blocks: dose response and efficacy/safety study. Ten patients received 15 mL of 1-2% morphine oral rinse. Of the 22 patients, serum morphine concentration was estimated in 5 representative patients.	Prospective randomized	Oral rinse with 2% morphine provides better pain relief as compared to 1% (80% *vs.* 60%, p=0.024). No systemically active detectable morphine concentration was observed.	One patient in the 1% group and 2 in the 2% group complained of a local side effect like burning/itching sensation.	Morphine oral rinse provides optimal pain relief without systemic absorption.

Table 1: Reported literature for use of morphine mouthwash for oral mucositis.

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utes. Thus, mouthwash may be repeated every 2 hourly along with other components of multimodal management.

To conclude, we suggest that morphine mouthwash may be considered as an effective management strategy as a part of multimodal treatment of oral mucositis in cancer patients receiving chemotherapy and/or radiation therapy. The effective pain relief may be achieved with 10-15 ml of 2% morphine aqueous solution and can be used 2-3 hourly as mouthwash in patients with mucositis pain.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Review

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Role of Steroids in Malignant Bowel Obstruction

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ABSTRACT

Various cancers such as ovarian, stomach, colon or pancreas may present with mechanical bowel obstruction. This may be partial or total depending on the pathology and extent of the disease. On presentation, the patient requires appropriate assessment and management as per underlying pathology and assessment findings. Comprehensive medical and surgical management strategies are required to manage malignant bowel obstruction effectively. Steroids have been reported for their beneficial use in malignant bowel obstruction. We review the usefulness of steroids in patients presenting with malignant bowel obstruction.

KEYWORDS: Malignant Bowel Obstruction (MBO); Steroids; Cancer.

ABBREVIATIONS: MBO: Malignant Bowel Obstruction; EC: Enterochromaffin; PEG: Percutaneous Endoscopic Gastrostomy; RCT: Randomized Controlled Trials; NCCN: National Comprehensive Cancer Network; BPCC: Bristol Palliative Care Collaborative.

INTRODUCTION

Bowel obstruction refers to functional or mechanical obstruction of the intestine which prevents physiological passage of food through the bowel. The bowel obstruction may be partial or complete and depends on the underlying pathology and extent of the disease. If such obstruction occurs due to malignancy, it is referred as malignant bowel obstruction (MBO). It can occur from an intraabdominal malignancy or related to malignancy with peritoneal involvement. The global prevalence of MBO is 3-15% of cancer patients.[1] MBO occurs more commonly in women (range: 59-69%),[1] and the age at presentation ranges from 58-65 years.[1,2] The time to manifestation of MBO from diagnosis of cancer is around 14 months (range 13-15 months).[1] The MBO occurs most commonly in the small bowel (61%) followed by the large bowel (33%) but may occur in both the small and large bowel simultaneously in 20% of patients.[2] MBO is seen in 20-50% of patients with ovarian cancer, 6-19% of stomach cancer patients, 6-13% of pancreatic cancer patients, and in 3-10% of patients with urinary bladder cancers.[1] Also, metastatic peritoneal deposits from breast cancer and melanoma lead to MBO in around 2-3% respectively.[1] The operative mortality (9-40%) and complication rates (9-90%) are very high with overall survival from 3-6 months.[2] The MBO related to mortality is observed in 15% of patients receiving palliative care.[3]

PATHOPHYSIOLOGY

The occurrence of MBO in cancer patients usually depends on the extent of disease and is more frequently seen in advanced cancers. MBO may occur because of extrinsic bowel compression, endoluminal bowel obstruction, intramural bowel infiltration, or extensive mesenteric infiltration.[1] Intra-luminal bowel tumor occludes the lumen of the bowel leading to obstruction and may also lead to intussusception. Intramural bowel tumor extending to mucosa may impair peristalsis or cause blockage of lumen.[2] Extramural obstruction occurs due to enlargement of tumor, mesenteric or omental masses or due to malignant adhesions or fibrosis. The neural

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infiltration like that of enteric or celiac plexus by the tumor may lead to severe impairment in peristalsis and consequent obstruction due to dysmotiliy.[1,2]

MBO leads to accumulation of fluid and gases causing bowel distension proximal to occlusive pathology.[1,3] This causes increased intra-luminal pressure and enhanced peristaltic contractions to overcome the obstruction causing colicky pain. Various inflammatory mediators are released including prostaglandins, vasoactive intestinal polypeptide and nociceptive mediators from the enterochromaffin (EC) cells of the intestine. These mediators lead to colicky pain, edema and hyperemia of bowel.[1] The obstruction is associated with an increase in intraluminal secretion of sodium, water and chlorides leading to nausea or vomiting. Vomiting leads to water and electrolyte losses.[3] It affects metabolic and hemodynamic status in such patients. Diagnosis is usually made by reviewing the history, comprehensive physical examination and radiological assessment.

MANAGEMENT

Various strategies for management of MBO include conservative medical management, surgical intervention or in certain cases combination of both.[2,3] The management is individualized based on clinical assessment and radiological findings with the understanding of background of underlying pathology. Management of MBO depends on the level of obstruction, disease extent, prior anticancer treatment, stage of cancer, prognosis, age, concurrent illness, presence of ascites, risk of repeat or multiple obstruction and patients health and performance status. The final management decision should include patient and family members in addition to palliative physician, gastroenterologist, interventional radiologist, and medical and surgical oncologist. A holistic multidisciplinary team approach with early involvement of the palliative care team is required to deal with the seriousness of the MBO.

The primary goal of MBO management is effective symptom control and improving quality of life.[4] The unmet desire of the patient to eat and enjoy a regular diet adds to psychological distress. At times, these patients may require palliative surgical diversion (diversion colostomy or ileostomy) for symptomatic control, especially in patients with large lesions and multiple areas of obstruction. Endoscopic stent placement and percutaneous endoscopic gastrostomy (PEG) placement are indicated in patients who are having poor physical status for surgery and refractory to medical management.[4]

Medical management is suitable for patients with MBO wherein expected survival is just weeks to days or in those who are poor surgical candidates.[5] The surgical intervention is not suitable in patients of MBO associated with carcinomatosis, palpable intraabdominal tumor mass with advanced disease, bowel obstructions at multiple sites, exposure to radiation therapy, and poor functional status.[5] The main aim of medical or surgical intervention is symptom management including control of nausea, vomiting, pain, maintenance of feeding, and optimization of biochemical abnormalities, thus allowing patients to be manageable at home with improved quality of life. Conservative management includes pharmacotherapy, intravenous fluid for hydration, nasogastric tube for decompression and psychosocial support.

The patient with MBO requires various pharmacological therapies for different purposes.[6] Opioids like fentanyl and morphine are used for pain management. Doses of opioids should be titrated per patient response, and there is no ceiling dose. Anticholinergics (hyoscine, scopolamine, glycopyrrolate) are used to slow peristaltic contractions.[6-8] Antisecretory drugs include thesomatostatin analogue (octreotide).[2,7,8] Antiemetics used include dopamine antagonists (haloperidol, metoclopramide, chlorpromazine), serotonin antagonist (ondansetron, granisetron) and steroids (dexamethasone).[2,7,8] The appropriate and timely medical management of MBO provides spontaneous resolution in more than one-third of patients.[2]

ROLE OF STEROIDS

The treatment targets three basic pathophysiologic consequences of MBO i.e. cascade of secretion, distension and bowel hypertonia associated with MBO.[6] Corticosteroids have been prescribed in palliative therapy since the late 1950's. They can be given by various routes including intravenous (i.v.), subcutaneous (s.c.), oral and rectal. The commonly used steroids include dexamethasone and methylprednisolone. The bioavailability of oral administration of dexamethasone is 80%.[9] Anti-inflammatory potency of dexamethasone is 5-10 times as that of methylprednisolone.

Steroids have a central antiemetic, anti-inflammatory, anti-secretory, analgesic and non-specific effect on general well-being when administered for MBO. They decrease gut wall edema, peritoneal inflammation and inflammation in proximity to the obstruction. They also decrease excretion of water and salt into the bowel lumen and thus indirectly decrease pain. Steroids decreased European Medicines Agency (EMA) at the site of bowel lumen obstruction due to tumor (extrinsic or intrinsic) and thus are beneficial in relieving MBO. Intestinal transit also improves because of decreased perineural edema and thus has bimodal benefit of both symptomatic relief and reduction in obstruction.[10] Thus, steroids hasten resolution of MBO and shorten length of hospital stay. Their general effect includes improved appetite, mood and strength as well.

The type of steroid, its dose and dosing schedule have been variously reported in literature. There is absence of recommendations for the specific steroid to be used and the specific dose for MBO. Below is a review of the existing literature for the use of steroids in MBO.

Studies Evaluating the Role of Steroids in MBO

Hardy et al[11] reported a randomized double blind placebo controlled trial in patients with gynecological cancer. He observed

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bowel obstruction resolution in 13 of 35 patients with 4 mg intravenously dexamethasone given every 6 hours (total 16 mg/day) for 5 days. Resolution of MBO occurred in 60% of patients. Side effects noted were gastrointestinal toxicity and abnormal perianal sensation. However, numbers of patients studied were too small for statistical analysis.[11]

Philip et al[12] reported a retrospective study in patients with gynecological cancer with MBO. They concluded that dexamethasone given in a dose of 8 mg/day intravenously or subcutaneously for a minimum of 3 days caused restoration of gastrointestinal function in 5 and symptomatic improvements in 4 patients out of total 13 patients. These effects were sustained for more than one month. The reduction in pain, nausea and vomiting with improved oral intake was observed in 69% patients in this study. However, absence of control group and very small sample size was limitation of this study.[12,13]

Laval et al[14] reported a randomized double-blind prospective study in patients with MBO. In this study, methylprednisolone 40 or 240 mg was administered once a day intravenously over 1 hour for 3 days. They concluded that out of 52 patients, 68% responded to treatment as compared to 33% on placebo. Outcomes were not statistically significant and because of the small sample size, no conclusion was made regarding dosage and efficacy.[14]

Laval et al[15] recommended use of steroids in peritoneal carcinomatosis with a dose of 1-4 mg/kg/day methylprednisolone and 0.25-1 mg/kg/day dexamethasone once a day intravenously or subcutaneously for a short course (5-10 days). They suggested steroids be started at the time of diagnosis and continued if symptoms improve or with resolution of bowel obstruction. Its long-term use is not recommended.[15]

META-ANALYSIS ON USE OF STEROIDS IN MBO

Feuer et al[16] reviewed 3 unpublished, randomized, placebo, double-blind controlled trials and 7 published (retrospective and prospective) trials. This meta-analysis reported that 6-16 mg intravenous dexamethasone per day was found to reduce the symptoms and resolve MBO in advanced gynecological and gastrointestinal cancer. Side effects were extremely low, but there was no survival benefit and the results were not statistically significant. This analysis also reported that six patients were needed to be treated for MBO with steroids to resolve one episode of bowel obstruction.[16,17]

A Cochrane review in 2008 analyzed 10 trials including 3 unpublished randomized controlled trials (RCT) and 7 published prospective and retrospective trials accountable for 89 patients.[17] They concluded that that the dose range 6-16 mg dexamethasone given intravenously or subcutaneously may bring about the resolution of bowel obstruction in 60% patients. The incidence of side effects is extremely low. However, it does not affect the length of survival.[17]

Studies Evaluating the Role of Steroids in Combination with Other Drugs in MBO

Mercadante et al[18] reported a study wherein he administered combination of metoclopramide, octreotide, steroids and amidotrizoate for MBO. The authors concluded these drugs an appropriate combination and doses provided symptom resolution in the palliative care setting. These drugs led to resolution of MBO along with improved intestinal mobility within 1-5 days and maintained bowel patency until death in most of the patients.[18]

Mercadante[19] studied combination of metoclopramide, octreotide and dexamethasone 12 mg intravenous infusion with amidotrizoate in MBO. He founded that out of 15 patients, 14 had recovery of intestinal transit within 1 to 5 days due to synergistic effect and vomiting resolved within 24 hours.[19]

Laval et al[20] observed that relief of MBO occurred with steroids along with antiemetic anticholinergic and analgesic when given for 5 days. They reported that 25 patients (31%) had symptomatic control without obstruction relief and 25 patients (31%) had resolution of MBO out of total 80 cases.[20] The dose of methylprednisolone use was 1-4 mg/kg/24 hours for 1hr intravenous infusion in the morning for 5 days or subcutaneously in 2 fractions in 2 different sites.

Murakami H et al[21] studied a combination of octreotide acetate and steroids in 19 patients with MBO. They observed that 13 patients out of 19 showed a marked resolution of the MBO, four patients showed a good response and no response was seen in 2 patients. They also reported that steroids increased the efficacy of octreotide for MBO symptom resolution.[21]

GUIDELINES FOR STEROID USE

According to National Comprehensive Cancer Network (NCCN) guidelines for palliative care, intravenous dexamethasone is to be given at a dose of 4 mg 3 to 4 times a day for MBO.[5] It should be stopped if no improvement occurs within 3-5 days.

Ahmad F[22] established current standards and guidelines for medical management of malignant bowel obstruction. He proposed that steroids are useful in patients with MBO for symptom management. He proposed that in patients with MBO, a 5-day trial of dexamethasone 8 mg once a day or 4 mg twice a day subcutaneously should be considered unless contraindicated.[22] Though the length of survival is not affected it improves the quality of life by symptom resolution. He also proposed that after administration of steroids for 48 hours, if the symptom resolves then the steroid should be tapered to lowest dose required to symptom control. Steroids should be discontinued if symptom improvement is not seen in 5 days of its administration.[22]

Bristol Palliative Care Collaborative (BPCC) steroid

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guidelines[23] have recommended 4-8 mg dose of dexamethasone in MBO.

DISCUSSION

Steroids are one of the drug classes prescribed for patients requiring palliative care for management of advanced malignancy for various symptom management.[24] Dexamethasone is relatively inexpensive, easily administered, well tolerated and may be given at home. Since steroids do have associated side effects, their use should be justified, used for minimum period and the minimal dose and its benefits should outweigh the adverse profile. Six mg of dexamethasone is comparable to 32 mg methylprednisolone and 40 mg prednisolone as equipotent doses.

Dexamethasone side-effects at dose range of 6-16 mg are minimal if used short-term, but the risk of gastrointestinal ulceration and immune suppression should be appropriately recognized and managed. Prophylactic gastric protection by a proton pump inhibitor should be advised. Common side effects include oral candidiasis, exacerbation of pre-existing diabetes, hypomania, agitation, hyperkinesia, peptic ulcer and insomnia. Total doses should be divided and given at breakfast and lunchtime to reduce psychotropic effects and insomnia. It is recommended that last dose of steroids be taken before 2 pm to reduce suppression of hypo-pituitary-adrenal axis.[25] The associated side effects of steroids need to be managed whenever prescribed in palliative care setting including good mouth care for prevention of oral thrush, ulcer prophylaxis and blood sugar control. Concurrent use of NSAIDS or bisphosphonates should be avoided. Since both agents, NSAIDs and steroids lead to gastric ulceration, their combination has been reported to have a 15 times greater risks for peptic ulcer disease as compared to patients who are not using these drugs alone.[26] The side effects of steroids are well documented and quite common. They should be rapidly tapered if no response is seen in 4-5 days.[27] Twycross reported that steroids may be started at higher dose and subsequently tapering to effect so as not to miss the response.[28] Or in other words, steroids, should be used at the lowest effective dose for the shortest period for symptom management in the palliative care setting.[26] According to clinical response, the dose of steroid should be reduced weekly. Long term side effects include increased susceptibility to infections, impaired wound healing, proximal myopathy, avascular bone necrosis, osteoporosis, excessive weight gain, cushingoid habitus and skin changes. They are contraindicated in active acute infections, psychosis and active peptic ulcer disease. Higher dose of steroids are recommended in those taking anticonvulsants such as phenytoin, carbamazepine, valproate and phenobarbitone as these drugs enhance the metabolism of corticosteroids.

Withdrawal of Steroids

Steroids should be withdrawn once their optimal effect has been achieved, suddenly or gradually based on patient response.

Abrupt withdrawal may be done in following situations[23,29,30]

- Dexamethasone dose <4-6 mg/day
- Dexamethasone <3 weeks treatment
- No recent repeated courses of steroids
- No risk of relapse of symptoms
- When adverse effects are not anticipated by abrupt withdrawal

Gradual withdrawal may be done in following situations[23,30]

- Dexamethasone dose >6 mg/day
- Dexamethasone >3 weeks treatment
- Patient has received second dose in evening
- History of repeated courses of systemic steroids
- Adreno-cortical insufficiency
- Risk of relapse of symptoms
- Patients who are taking a short course within 1 year of stopping long term therapy

For gradual withdrawal, if the dose of dexamethasone is more than 2 mg daily, it should be halved every 3-5 days until reaching 2 mg. If dose of dexamethasone used is less than 2 mg/day, dose should be reduced by 0.5-1 mg every 5-7 days.[23] Initially, the dose of steroids should be reduced rapidly i.e. reducing to half every day so as to reach a physiological requirement i.e. dexamethasone 1-2 mg/24 h or prednisolone 7.5 mg/24 h. Subsequently, more gradual reduction is advised. If the symptoms are steroid responsive, it may be continued at a set minimal dose for a maximum of 2-4 weeks. However, the symptom and side effect profile of steroids should be reviewed regularly for early stoppage. If symptom recurs during dose reduction, the dexamethasone dose may be increased back to dose at which symptoms were controlled.[30]

The issues related to steroid withdrawal also include hypo-adrenal crisis–malaise, profound weakness, hypotension, nausea and vomiting, anxiety, terminal restlessness etc. Hence, staged withdrawal with monitoring of these symptoms requires attention and management. Gradual reduction reduces the risk of symptom recurrence and gives time for intrinsic production of steroids to recommence.

CONCLUSION

MBO is a seen in palliative care settings commonly in specific types of malignancies. However, there is no definitive standardized evidence-based medical management protocol or guidelines. Various administration routes, optimal doses, duration and type of steroids are yet to be standardized. The existing literature is scarce especially the well conducted prospective randomized studies. The clinical trials reported are having small size, methodological flaws and without statistical significance. Because of intermittent nature of early symptoms associated MBO, it is

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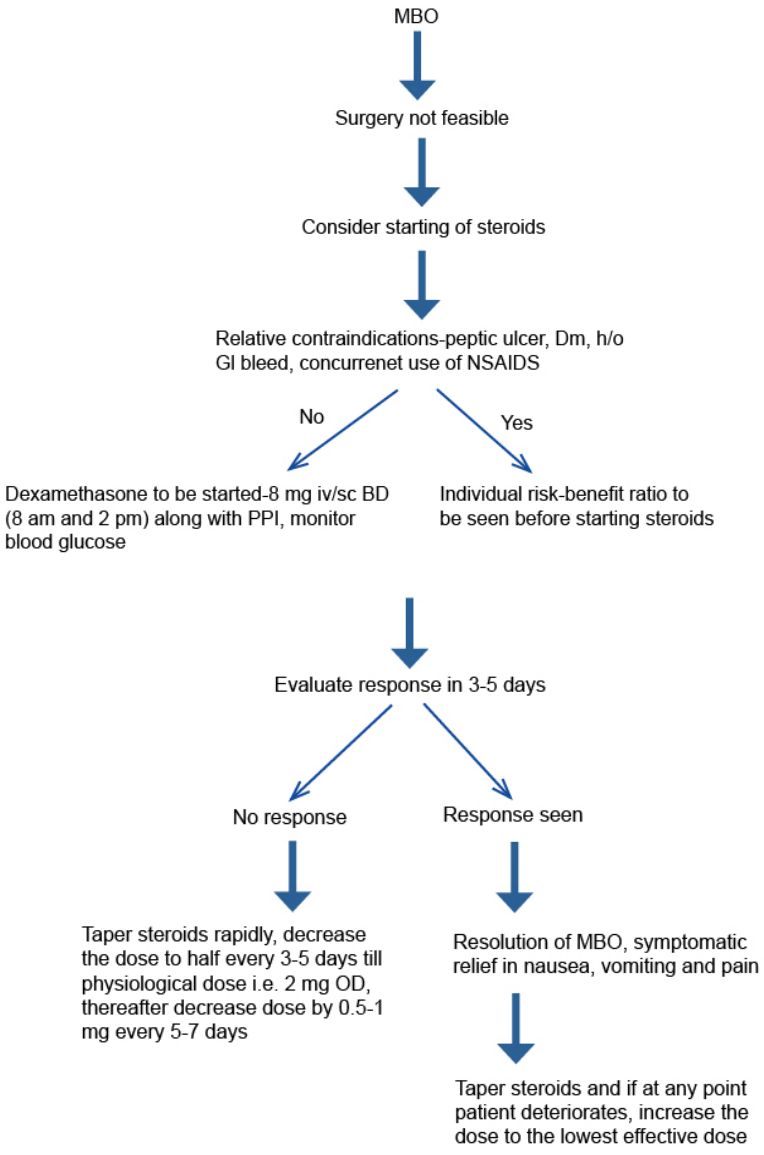

Figure 1: Role of steroids for MBO management.

difficult to attribute resolution of symptoms to steroids. However, the existing literature favors the early use of steroids in patients with MBO. Further, studies and research in large scale is required to statistically prove the efficacy of dexamethasone.

SUGGESTIONS

Based on published literature, it is suggested to start subcutaneous or intravenous dexamethasone in dose of 8 mg twice a day at 8 am and 2 pm after meals under gastrointestinal prophylaxis for 5 days in patients with MBO with non-feasibility of surgery (Figure 1). Regular assessment and documentation of the response should be done. If no response occurs in 5 days, it should be tapered off quickly. If resolution of bowel obstruction or symptomatic improvement occurs, it should be continued but dose should be tapered to lowest dose required clinically. General principle of steroid use is-the lowest effective dose for the least possible time. Multimodal treatment of MBO is recommended including anticholinergic, antiemetic, anti-secretory and steroids.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Research

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A Feasibility Study to Investigate the Effect of Nutritional Support for Advanced Cancer Patients in an Inpatient Hospice in Japan

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ABSTRACT

Backgrounds: There has been no prospective study to investigate the effect of nutritional support for advanced cancer patients in inpatient hospices. Therefore, we conducted a prospective observational study to explore the feasibility of investigating the effect of nutritional support for advanced cancer patients in an inpatient hospice.
Methods: We prospectively collected the following data: performance status, results of blood tests, calorie and protein intake, body weight, skeletal muscle mass, and Functional Assessment of Anorexia/Cachexia Therapy (FAACT) on the 1st day of admission and every 2 weeks. All patients were followed-up to their discharge or 4 weeks. Primary endpoint was percentage of patients who completed the intervention. Secondary endpoints were overall survival and improvement of Karnofsky Performance Status (KPS) in the 2nd week. Subgroup analysis was performed by dividing patients into 3 groups with change of KPS in the second week (improving, maintaining, and deteriorating KPS groups).
Results: A total of 43 patients met the inclusion criteria, and among them, 14 refused to participate. Thus, 29 were analyzed in the present study**.** The percentage of patients who completed the intervention in the 2nd week was 93.1% and in the 4th week 44.8%. Sixteen patients, 55.2%, were alive 4 weeks. The KPS improvement rate was 41.4%. The 29 patients were divided into improving KPS (n=12), maintaining KPS (n=9), and deteriorating KPS (n=8). All patients in improving KPS and 4 patients in maintaining KPS were alive 4 weeks. Survival decreased with deterioration of KPS (p<0.001). Calorie/protein sufficiency rate and FAACT score of patients in improving KPS group temporarily improved in the 2nd week.
Conclusions: This study indicated the feasibility of conducting trials to investigate the effect of nutritional support for advanced cancer patients in an inpatient hospice.

KEYWORDS: Advanced cancer patient; Inpatient hospice; Nutritional support; Feasibility; Cancer cachexia.

ABBREVIATIONS: FAACT: Functional Assessment of Anorexia/Cachexia Therapy; KPS: Karnofsky Performance Status; PPI: Palliative Prognostic Index; IRB: Institutional Review Board; MHLW: Ministry of Health, Labor and Welfare; BEE: Basal Energy Expenditure; BIA: Bioelectrical Impedance Analysis; BMI: Body Mass Index.

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INTRODUCTION

A great number of advanced cancer patients are suffering from physical and psychosocial burdens due to cancer cachexia.[1-3] Involuntary weight loss, a main symptom of cancer cachexia, often follows anorexia and declining food intake, and thus these are causes of distress for patients.[1-3] Involuntary weight loss links to the deterioration of performance status, quality of life (QoL), nutritional status, treatment outcomes, and survival in advanced cancer patients.[4-9] However, there is limited data from randomized controlled trials (RCT) about the treatment of cachexia in advanced cancer patients,[4-9] while several studies have revealed the potential benefits of reversing or delaying progressive tissue wasting.[10-14] In addition, currently, a consensus that nutritional support is important to treat malnutrition due to cancer cachexia is growing.[15] In advanced cancer patients, effects of increased calorie intake and long-term nutritional support have been rarely investigated, and the role of nutritional support to alleviate the negative impact of cancer cachexia has not been clarified.[9,16] Furthermore, to the best of our knowledge, there has been no prospective study to investigate the effect of nutritional support for advanced cancer patients in inpatient hospices. Therefore, we conducted a prospective observational study to explore the feasibility of investigating the effect of nutritional support for advanced cancer patients in an inpatient hospice.

METHODS

The present study was conducted in an inpatient hospice at Osaka City General Hospital (Osaka, Japan) between October 2014 and September 2015.

Consecutive eligible patients were recruited for the study if they had been newly referred to the inpatient hospice during the study period. Inclusion criteria were as follows: (1) adult patients with histologically proven incurable malignancies, (2) no cognitive impairment at admission, (3) Karnofsky Performance Status (KPS)[17] of 30 or more at admission, and (4) Palliative Prognostic Index (PPI)[18] of 6.0 or less at admission. If the PPI score is greater than 6.0, survival is less than 3 weeks (sensitivity-80%; specificity-85%).[18]

Patient demographics and clinical characteristics, including age, gender, site of primary cancer, and metastatic disease, were obtained. We evaluated and recorded patients' performance status, results of blood tests, calorie and protein intake, body weight, and skeletal muscle mass on the 1st day of admission and every 2 weeks. Scores of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire,[19] which has been validated to assist clinicians in testing the efficacy of anti-anorexia/cachexia therapies, were collected as well. A higher score on the FAACT questionnaire indicates better quality of life. All patients were followed-up to their discharge or 4 weeks after their enrollment.

Primary endpoint was percentage of patients who completed the intervention. Secondary endpoints were overall survival and improvement of KPS score in the 2nd week. We defined improved KPS score as an increase by 20 points or more, deteriorated score as a decrease by 20 points or more, and other changes in score as maintaining. Subgroup analysis was performed by dividing patients into 3 groups with regard to their changes of KPS score in the 2nd week (improving, maintaining, and deteriorating KPS groups). Overall survival was compared and changes in nutrition indexes, calorie and protein intake, and quality of life (i.e., FAACT scores) were also investigated between the 3 groups.

The present study was conducted in accordance with the ethical standards of the Helsinki Declaration and the ethical guidelines for epidemiological research established by the Ministry of Health, Labor and Welfare (MHLW) in Japan, and approved by the Institutional Review Board (IRB) at Osaka City General Hospital. We obtained written informed consent before enrolling participants.

Interventions

As a part of routine clinical practice in our inpatient hospice, attending physicians ask patients whether they want to receive help from a nutritional support team. In the present study, if the patient agreed to receive such help, a nutritional support team, consisting of trained physicians, dietitians, pharmacists, and nurses, provided individualized and tailored nutritional support to the patient. When the amount of oral intake of the patient was under half, the patient was monitored daily. The goal of the nutritional support was to meet or exceed the energy and protein requirements of the Nordic recommended allowances[20] (daily energy intake in the range of 1.5-1.7×basal energy expenditure (BEE), calculated from the Harris-Benedict equation,[21] and protein intake of 1.0-1.2 g/kg body weight). The intervention included the following: (1) exploring the causes of malnutrition (e.g., decreased oral intake, hypermetabolism); (2) palliating symptoms (e.g., anorexia, nausea, vomiting, constipation, diarrhea, odynophagia, dysphagia); (3) giving patients explanations on cancer cachexia, encouraging patients with feeding, and supporting the nurses in this role; (4) offering dietary foods and supplements, including high omega-3 fatty acids and branched chain amino acids; and (5) administering total parenteral nutrition or peripheral parenteral nutrition, if indicated and agreed to.

Body Composition Analysis

We introduced body composition analysis into nutritional assessment using bioelectrical impedance analysis (BIA). BIA measures the body's resistance to flow (impedance) of alternating electrical current at a designated frequency between points of contact on the body. Water in body tissue is conductive; therefore, the measurement of body impedance can indirectly provide information on the body's tissue content, including total body water, fat-free mass, and skeletal muscle mass.[22-24]

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In preparation for BIA, patients fasted for at least 3 hours and voided immediately before starting the analysis. By using the InBody 770 (InBody Japan, Tokyo, Japan), various parameters, including body weight and skeletal muscle mass, can be automatically and simultaneously measured within 1 minute. The skeletal muscle mass is shown as a percent against the standard calculated by age, sex, and height of each patient. The normal skeletal muscle mass range is 90-110% of the standard. In the present study, we calculated the decrease rate of skeletal muscle mass as (the lower limit of the normal-the measured value)/the lower limit of the normal×100.

Statistical Analysis

Comparisons were performed using the Kruskal-Wallis test. Survival after enrollment was investigated by the Kaplan-Meier method. All results were considered to be statistically significant if the *p* value was less than 0.05. All analysis was performed using IBM SPSS v. 22.0 (SPSS Inc., Chicago, IL, USA).

We calculated sample size needed as follows: given 80% of completion rate this intervention was feasible, adequate sample size was 39 with interval of 0.25 both side in 95% confidence interval (CI).

RESULTS

In the present study, 344 consecutive patients newly referred to the inpatient hospice during the study period were enrolled. A total of 43 patients met the inclusion criteria, and among them, 14 refused to participate. Thus, 29 were analyzed in the present study. Patient characteristics are shown in Table 1. Mean age was 69.6±6.8 years old, and male gender accounted for 62.1%. The top sites of primary cancer were the lung, upper and lower gastrointestinal tracts, and biliary system and pancreas. The distribution of KPS scores was as follows: 100-80, 3.4%; 70-50, 86.2%; and 40-30, 10.3%.

The percentage of patients who completed the interven-

	Total (n=29)	Improving KPS (n=12)	Maintaining KPS (n=9)	Deteriorating KPS (n=8)	*p*
Age (years)	69.6±6.8	68.7±7.0	70.7±7.0	69.8±6.9	0.802
Male gender	18 (62.1%)	6 (50.0%)	6 (66.7%)	6 (75.0%)	0.511
Site of primary cancer					
Lung	10 (34.5%)	4 (33.3%)	3 (33.3%)	3 (37.5%)	0.892
Upper and lower gastrointestinal tracts	7 (24.1%)	4 (33.3%)	0 (0.0%)	3 (37.5%)	
Biliary system and pancreas	5 (17.2%)	0 (0.0%)	5 (55.6%)	0 (0.0%)	
Breast	3 (10.3%)	3 (25.0%)	0 (0.0%)	0 (0.0%)	
Urological	2 (6.9%)	1 (8.3%)	0 (0.0%)	1 (12.5%)	
Head and neck	1 (3.4%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	
Hematological	1 (3.4%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	
Metastatic disease					
Bone	15 (51.7%)	8 (66.7%)	2 (22.2%)	5 (62.5%)	0.109
Lung	9 (31.0%)	4 (33.3%)	3 (33.3%)	2 (25.0%)	0.913
Brain	8 (27.6%)	3 (25.0%)	3 (33.3%)	2 (25.0%)	0.901
Liver	7 (24.2%)	1 (8.3%)	4 (44.4%)	2 (25.0%)	0.170
Body mass index (kg/m^2)	20.1±3.2 (n=26)	20.4±2.8	21.2±3.5 (n=8)	18.1±3.1 (n=6)	0.180
Decrease rate of skeletal muscle mass	-9.5±15.8 (n=23)	-5.0±15.8 (n=11)	-9.3±16.6 (n=6)	-18.2±14.0 (n=6)	0.151
Palliative prognostic index	3.5±1.3	3.1±1.4	3.8±1.2	3.6±1.2	0.440
KPS					
100-80	1 (3.4%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	0.096
70-50	25 (86.2%)	10 (83.3%)	8 (88.9%)	7 (87.5%)	
40-30	3 (10.3%)	2 (16.7%)	1 (11.1%)	0 (0.0%)	
Serum concentrations					
Hemoglobin (g/dl)	10.7±2.4	11.1±2.5	10.1±2.2	10.8±2.5	0.718
Total lymphocyte count (/μl)	1300±692	816±306	1740±596	1530±812	0.002
Albumin (g/dl)	2.9±0.5	3.0±0.4	2.7±0.6	3.0±0.4	0.292
Transthyretin (mg/dl)	13.6±6.9	16.2±7.4	11.5±5.1	12.0±7.5	0.232
C-reactive protein (mg/dl)	3.8±3.5	3.3±4.5	4.6±3.2	3.7±2.0	0.203

Values represent mean±standard deviation or n (%) where appropriate.
KPS: Karnofsky Performance Status.

Table 1: Baseline patient characteristics.

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tion in the 2nd week was 93.1% (95% CI 78-98%), and that in the 4th week was 44.8% (95% CI 28-63%), in other words, the end-of-study attrition rate was 55.2% (95% CI 37-72%). Sixteen patients out of 29, 55.2% (95% CI 37-72%), were alive 4 weeks after their enrollment. Two patients died within 2 weeks, and 3 patients were discharged to home and 11 patients died between the 3rd and 4th weeks. Patients flow through the study is outlined (Figure 1). The KPS improvement rate in the second week was 41.4% (95% CI 25-59%), while the maintained rate and deterioration rate were 31.0% (95% CI 17-49%) and 27.6% (95% CI 15-46%), respectively.

We then divided the 29 patients into 3 groups with regard to their changes of KPS score in the 2nd week: improving KPS group (n=12), maintaining KPS group (n=9), and deteriorating KPS group (n=8). All items, except for total lymphocyte count, were not significantly different between the 3 groups (Table 1).

Waterfall plots of changes in KPS from baseline to the 2nd week are shown in Figure 2. In the improving KPS group, all of the 12 patients were alive 4 weeks after their enrollment and 3 patients were discharged to home between the 3rd and 4th weeks. In the maintaining KPS group, 4 patients were alive 4 weeks after their enrollment and 5 patients died between the 3rd and 4th weeks. In the deteriorating KPS group, 2 patients died within 2 weeks and 6 patients died between the 3rd and 4th weeks.

Kaplan-Meier survival curves for overall survival of the 3 groups are shown in Figure 3. Survival after enrollment decreased with deterioration of KPS score. The difference in survival rates between the 3 groups was statistically significant ($p<0.001$).

Changes in KPS, nutrition indexes, calorie and protein intake, and FAACT scores are shown in Table 2. Concerning body mass index (BMI), all values in the improving KPS group

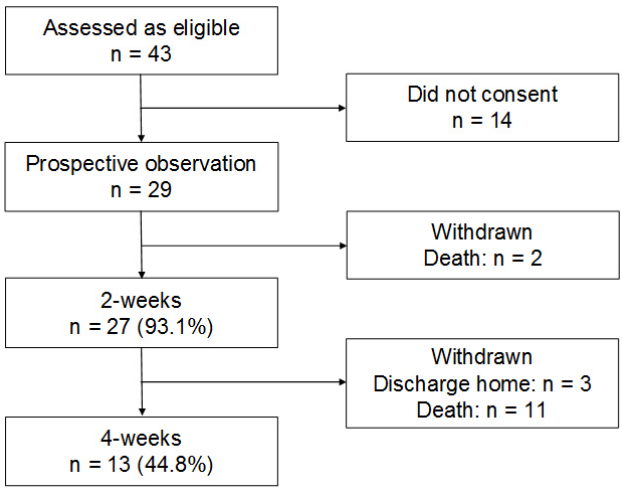

Figure 1: Patients flow through the study. The percentage of patients who completed the intervention in the second week was 93.1% (95% CI 78-98%), and that in the 4th week was 44.8% (95% CI 28-63%). Sixteen patients out of 29, 55.2% (95% CI 37-72%), were alive 4 weeks after their enrollment. Two patients died within 2 weeks, and 3 patients were discharged to home and 11 patients died between the 3rd and 4th weeks.

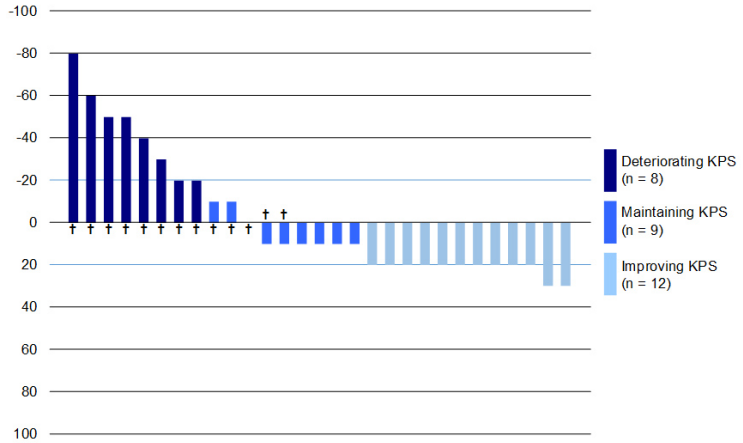

Figure 2: Waterfall plots of changes in Karnofsky Performance Status (KPS) from baseline to the 2nd week are shown. The improvement rate in KPS in the 2nd week was 41.4% (95% CI).

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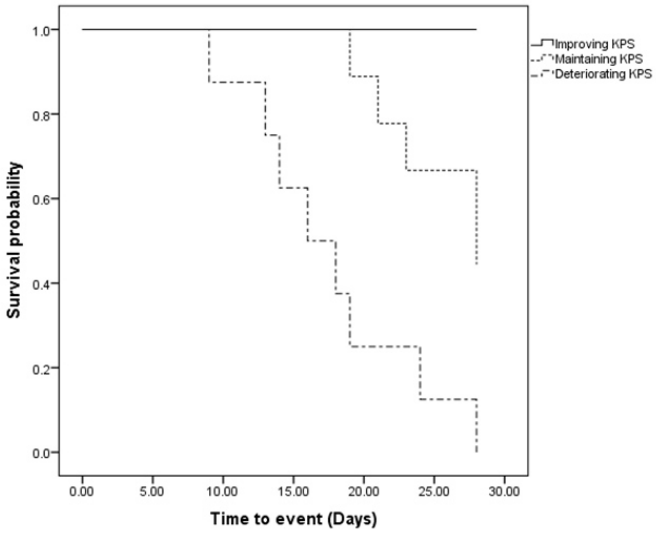

Figure 3: Kaplan-Meier plot (Log-rank p<0.001)
Kaplan-Meier survival curves for overall of three groups: the improving karnofsky performance status (KPS) group (n=2), the maintaining KPS group (n=8). Survival after enrollment decreased with deteriorating KPS (n=8). Survival after enrollment decreased with deteriorating KPS. The difference in survival rates among the three groups was statistically significant (p<0.001).

		Baseline	2-weeks	4-weeks
KPS	Total (n=29)	50 (40-80) (n=29)	60 (0-90) (n=29)	10 (0-80) (n=26)*
	Improving KPS (n=12)	50 (40-70) (n=12)	80 (60-90) (n=12)	50 (10-70) (n=9)*
	Maintaining KPS (n=9)	50 (40-70) (n=9)	60 (40-70) (n=9)	10 (0-80) (n=9)
	Deteriorating KPS (n=8)	70 (50-80) (n=8)	20 (0-50) (n=8)	0 (0-10) (n=8)
Body mass index (kg/m^2)	Total (n=29)	20.1±3.2 (n=26)	20.3±2.8 (n=19)	20.8±3.1 (n=7) *
	Improving KPS (n=12)	20.4±2.8 (n=12)	20.5±2.7 (n=12)	20.4±3.2 (n=6) *
	Maintaining KPS (n=9)	21.2±3.5 (n=8)	20.0±3.4 (n=6)	23.3±0.0 (n=1)
	Deteriorating KPS (n=8)	18.1±3.1 (n=6)	18.8±0.0 (n=1)	
Decrease rate of skeletal muscle mass (%)	Total (n=29)	-9.5±15.8 (n=23)	-8.3±15.2 (n=15)	-9.8±6.6 (n=6)*
	Improving KPS (n=12)	-5.0±15.8 (n=11)	-5.9±14.8 (n=12)	-9.8±6.6 (n=6)*
	Maintaining KPS (n=9)	-9.3±16.6 (n=6)	-18.1±15.1 (n=3)	
	Deteriorating KPS (n=8)	-18.2±14.0 (n=6)		
Total lymphocyte count (/μl)	Total (n=29)	1300±692 (n=29)	1314±714 (n=25)	1176±651 (n=16)*
	Improving KPS (n=12)	816±306 (n=12)	976±364 (n=12)	892±285 (n=9)*
	Maintaining KPS (n=9)	1740±596 (n=9)	1886±862 (n=9)	1587 ±889 (n=6)
	Deteriorating KPS (n=8)	1530±812 (n=8)	1043±273 (n=4)	1273±0 (n=1)
Albumin (g/dl)	Total (n=29)	2.9±0.4 (n=29)	2.7±0.6 (n=25)	2.7±0.7 (n=15)*
	Improving KPS (n=12)	3.0±0.4 (n=12)	2.9±0.4 (n=12)	2.8±0.4 (n=9)*

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	Maintaining KPS (n=9)	2.7±0.6 (n=9)	2.6±0.7 (n=9)	2.6±0.9 (n=6)
	Deteriorating KPS (n=8)	3.0±0.4 (n=8)	2.6±0.4 (n=4)	
Transthyretin (mg/dl)	Total (n=29)	13.6±6.9 (n=29)	13.8±6.3 (n=25)	12.1±7.4 (n=15) *
	Improving KPS (n=12)	16.2±7.4 (n=12)	15.6±6.0 (n=12)	12.9±7.7 (n=9) *
	Maintaining KPS (n=9)	11.5±5.1 (n=9)	14.0±6.1 (n=9)	10.9±7.5 (n=6)
	Deteriorating KPS (n=8)	12.0±7.5 (n=8)	7.8±5.4 (n=4)	
C-reactive protein (mg/dl)	Total (n=29)	3.8±3.5 (n=29)	5.0±5.5 (n=25)	7.0±7.1 (n=16) *
	Improving KPS (n=12)	3.3±4.5 (n=12)	2.8±2.8 (n=12)	5.2±4.8 (n=9) *
	Maintaining KPS (n=9)	4.6±3.2 (n=9)	6.0±5.9 (n=9)	9.3±10.0 (n=6)
	Deteriorating KPS (n=8)	3.7±2.0 (n=8)	9.6±8.5 (n=4)	9.38±0.0 (n=1)
Calorie /protein sufficiency rate (%)	Total (n=29)	56.0±24.7/71.3±35.2 (n=29)	64.1±36.6/75.5±45.4 (n=27)	56.4±43.1/63.9±48.6 (n=16)*
	Improving KPS (n=12)	62.2±25.6/77.4±39.3 (n=12)	89.8±16.2/105.8±25.1 (n=12)	55.6±39.4/62.6±47.4 (n=9)*
	Maintaining KPS (n=9)	60.0±24.4/77.0±34.1 (n=9)	63.8±29.0/75.5±36.3 (n=9)	66.4 ±4 9.0/76.6±49.7 (n=6)
	Deteriorating KPS (n=8)	42.0±20.6/55.9±28.7 (n=8)	13.1 ±18.1/15.1±25.6 (n=6)	3.3±0.0/0.0±0.0 (n=1)
FAACT, Total/ Anorexia cachexia subscale	Total (n=29)	76.6±14.5/22.6±7.8 (n=29)	78.0±19.6/24.1±9.9 (n=22)	68.8±16.6/20.9±10.3 (n=11)*
	Improving KPS (n=12)	77.2±18.5/21.0±7.4 (n=12)	81.8±21.4/25.2 ±10.6 (n=12)	66.1±12.6/19.1±8.9 (n=7)*
	Maintaining KPS (n=9)	82.1±11.1/25.2±8.9 (n=9)	75.9±17.9/23.8±10.4 (n=8)	73.5±23.6/24.0±13.1 (n=4)
	Deteriorating KPS (n=8)	69.5±8.3/21.9±7.2 (n=8)	63.5±12.0/19.0±2.8 (n=2)	

Values represent median (range) or mean±standard deviation.
*: In the improving KPS group 3 patients were discharged to home between the third and fourth weeks.
KPS: Karnofsky Performance Status, FAACT: The Functional Assessment of Anorexia/Cachexia Therapy.

Table 2: Changes in KPS, nutrition indexes, calorie and protein intake, and scores of FAACT.

and maintaining KPS group were over 20.0 kg/m^2 throughout the study. Concerning the decrease rate of skeletal muscle mass, all values in the improving KPS group were under 10.0% throughout the study. Changes in total lymphocyte count were inconsistent. Although changes in albumin and transthyretin (TTR) trended downward, the values of transthyretin in the 2nd week of patients in the maintaining KPS group temporarily increased. Although changes in C-reactive protein trended upward, the values in the second week of patients in the improving KPS group temporarily decreased. Calorie/protein sufficiency rate in the second week of patients in the improving KPS group temporarily increased, while that in the deteriorating KPS group highly decreased. Scores of FAACT in the 2nd week of patients in the improving KPS group slightly improved.

DISCUSSION

To the best of our knowledge, this is the 1st report of a prospective observational study to explore the feasibility of investigating the effect of nutritional support for advanced cancer patients in an inpatient hospice.

The present study indicates the feasibility of conducting trials to investigate the effect of nutritional support for advanced cancer patients in an inpatient hospice. Especially, the percentage of patients who completed the intervention in the second week was 93.1% (95% CI 78-98%). The end-of-study attrition rate was 55.2% (95% CI 37-72%), similar to the result of a previous study,[25] where it was 44% (95% CI 41-47%).

We must take into account frailty and short survival in advanced cancer patients in designing multicenter randomized controlled trials in palliative care settings. Values of KPS, blood tests, and calorie/protein sufficiency rate are more easily obtained than those of body mass index and decrease rate of skeletal muscle mass, because patients with impending death are incapable of measurement of body weight and skeletal muscle mass. Therefore, we consider that improvement of KPS score in the second week is a candidate for a primary endpoint to minimize patient withdrawal due to death and progression of the

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underlying disease, despite the possibility of underestimation the effects of nutritional support due to short observation periods. Furthermore, KPS is often affected by many other issues (e.g. treatment of any reversible conditions unrelated to cancer cachexia such as pneumonia) in addition to cancer cachexia, while KPS is associated with nutritional and general status of advanced cancer patients and is one of the most important factors to estimate them.

Results of the present study imply that advanced cancer patients who recover their performance status may have longer survival than those who do not, and that increased calorie and protein intake by nutritional support may be linked to improvement in their performance status and quality of life. However, the association between calorie and protein intake, performance status, and skeletal muscle mass is unclear as well as the determinants of improving performance status and quality of life in advanced cancer patients.

Skeletal muscle depletion has been uniformly a strong predictor of survival independent of age, gender, stage, disease site, and performance status in cancer patients.[26-28] Tailored nutritional support for selective advanced cancer patients with the aim of keeping or gaining skeletal muscle mass, a kind of individualized anti-cancer cachexia therapy, may be linked to better performance status and longer survival even in palliative care. In addition, it is necessary to consider the influence of age and gender on performance status and skeletal muscle mass. Skeletal muscle depletion is associated with aging in cancer patients,[29] while the results on gender of previous studies have been inconsistent. A study of advanced cancer patients concluded that gender was not related to muscle wasting or gain,[30] while male pancreatic cancer patients lost more muscle and at an accelerated rate compared with females.[31]

Further research is needed to examine the relationship between nutritional support and influence of age and gender on performance status and skeletal muscle mass in advanced cancer patients.

There are several limitations to be acknowledged. First, the findings are not definitive and cannot be generalized because it was a single-arm and single-institution study with a modest sample size. This was a preliminary study, and a RCT to reveal the effect of nutritional support for advanced cancer patients is warranted. Second, there might be heterogeneity of intervention and patient reaction. The intervention included encouraging patients with feeding, offering dietary foods and supplements, and administering parenteral nutrition; hence, the effects of oral nutritional supplementation and those of parenteral nutrition were mixed. We believe that the clinical implications were not affected, however, because we administered "supplemental" parenteral nutrition to patients who became unable to take sufficient nourishment orally as usual care. Third, several subjects consumed supplements, including high omega-3 fatty acids and branched chain amino acids. The use of these supplements for formulation may lead to gaining skeletal muscle mass; the effects of these should therefore be taken into consideration. Fourth, alleviating symptoms might have contributed to improvement in performance status. However, we believe that the clinical implications were not affected, because we usually do our best to alleviate symptoms for every patient as a part of routine clinical practice in an inpatient hospice. Fifth, the effects of long-term nutritional support for advanced cancer patients are unclear due to the 4 weeks of observation in the present study. Finally, we initially calculated sample size needed as follows; given 80% of completion rate this intervention was feasible; adequate sample size was 39 with interval of 0.25 both side in 95% confidence interval. Actually due to difficulty in recruitment, this study was ended after a total of 29 patients were recruited.

CONCLUSION

The present study indicates the feasibility of conducting trials to investigate the effect of nutritional support for advanced cancer patients in palliative settings as well as the potentiality of the effect of nutritional support for them. Further research should be conducted in the near future.

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CONFLICTS OF INTEREST

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