Development of Palliative Medicine for Cancer Patients in Japan: From Isolated Voluntary Effort to Integrated Multidisciplinary Network

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The paradigm of palliative care in cancer medicine has shifted from only care of terminally ill patients to earlier intervention for them in the recent 15 years. The concept of palliative medicine was founded in Japan in the 1970s. During the past 15 years, various new drugs and interventions have been introduced mainly for pain control, which is one of the major problems in the area of palliative medicine in cancer. According to the aim of the Cancer Control Act established in Japan (2006), patients and their families will be able to access easily integrated high-quality cancer care wherever they live at the time of 2016. Systematic and continuous education for medical staff is mandatory, and a major breakthrough for achieving this purpose would be to increase the number of courses and faculties in palliative medicine at most universities in Japan.

Key words: palliative care – pain control – network of home care

DEFINITION OF PALLIATIVE MEDICINE AND NOTES OF TERMINOLOGY

The paradigm of palliative medicine in cancer patients has shifted in the recent 15 years. Palliative care is an approach that improves the quality of life (QOL) of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification/assessment and treatment. Issues to cover in palliative medicine are pain and other problems, such as physical, psychological and spiritual (World Health Organization: WHO 2002) (1). Early and accurate detection of patients’ problems is a key issue for supporting them with efficient and timely management. Relief with treatment and prevention of suffering symptoms are the most important objectives in palliative care for cancer patients and their families (Table 1). In 1989, the WHO defined palliative medicine as the active total care of patients whose disease is not responsive to curative treatment. The goal of palliative care is defined as the achievement of the best possible QOL for terminally ill patients and their families in a former statement. The paradigm of palliative medicine has shifted from the care of terminally ill cancer patients alone to earlier intervention in order to maintain better QOL of patients.

The phrase ‘terminal care’ has been used in England from 1950 (2). It means to understand and respect the patient’s dying process and to care for them with humanity. ‘Hospice care’ aims to lessen the burden of terminally ill patients and to keep the end of their life peaceful and quiet. Hospice care began originally in England in the 1970s. The term ‘Palliative Care’ itself means to expand the theory of hospice care and to relieve suffering symptoms by offering treatments, starting in communities in Canada in the 1980s. ‘Supportive care’ indicates a more broad meaning including to reduce or to prevent various adverse reactions of cancer treatments, such as chemotherapy-induced nausea and vomiting, and febrile neutropenia after administration of chemotherapeutic agents. It has developed with innovative drugs introduced to supportive care since 1980s. ‘End-of-Life care’ contains care for both cancerous and non-cancerous patients expanding in North America in the 1990s. It indicates total care for geriatric patients. ‘Palliative Medicine’ itself means an area of medical science focusing both on clinical practice and on research that covers palliative care.
Table 1. Aim of cancer palliative care

<table>
<thead>
<tr>
<th>Aim of Cancer Palliative Care</th>
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<tr>
<td>Provides relief from pain and other distressing symptoms</td>
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<tr>
<td>Affirms life and regards dying as a normal process</td>
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<td>Intends neither to hasten or postpone death</td>
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<td>Integrates the psychological and spiritual aspects of patient care</td>
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<td>Offers a support system to help patients live as actively as possible until death</td>
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<td>Offers a support system to help the family cope during the patients illness and in their own bereavement</td>
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<tr>
<td>Uses a team approach to address the needs of patients and their families, including bereavement counseling, if indicated</td>
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<td>Will enhance quality of life and may also positively influence the course of illness</td>
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<tr>
<td>Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications</td>
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HISTORY OF PALLIATIVE MEDICINE IN CANCER PATIENTS IN JAPAN

In Japan, the concept of palliative medicine was founded back to the 1970s. Emeritus Professor Tetsuo Kashiwagi at Osaka University developed an integrated care system for terminally ill cancer patients at the Yodogawa Christian Hospital in Osaka in 1972. He is a psychiatrist and a pioneer of palliative medicine both in clinical and educational setting in Japan. He has been an opinion leader in founding the Japanese Society of Palliative Medicine (JSPM) and currently is the auditor of the society. In 1970, Professor Kouichi Bai at Kitasato University introduced and explained the term ‘Informed Consent’ to Japanese clinical medicine for the first time in his lecture text. In the late 1970s, Japanese physicians focused on the importance of the care of terminally ill cancer patients. In 1977, the aim and activity of St Christopher’s Hospice in the UK was first introduced by the press in Japan. In 1981, the first Japanese hospice was established by Dr. Yoshio Hara at the Seirei Mikatagahara Hospital in Hamamatsu City. Dr. Fumikazu Takeda, a neurosurgeon and the emeritus president of Saitama Cancer Center Japan, spreads the methods of treating cancer pain intensively with anti-analgesics in the late 1970s. In 1982, he attended the experts’ consensus conference in Italy as the only representative from Japan. He was encouraged by the exciting discussion at the conference and introduced the concept of ‘Steps of the WHO ladder’ in pain control in Japan. He has enlightened medical staff on the proper use of opioids in patients who suffer severe cancer pain in various areas of Japan, like a missionary. In 1989, the task-force meeting of the Japanese Ministry of Health Labor and Welfare (MHLW) for ‘Palliative care for terminally ill cancer patients’ published a report. This report was the first standard guideline for palliative care focusing on terminally ill cancer patients. The Japanese MHLW introduced reimbursement in health insurance for palliative cancer care at a specially equipped ward in 1990. In 1991, the Society of Domestic Hospice and Palliative Care Staff was started and expanded currently as the non-profit organization Hospice and Palliative Care Japan (NPO-HPCJ). In 1992, the bioethics committee of the Japan Medical Association reported a proposal on general guidelines of terminal care for patients with non-curative and progressive diseases.

In 1996, the JSPM was organized with about 200 founding members including Emeritus Professor Tetsuo Kashiwagi (3). In the early 2000s, the society got approval as an NPO and it currently consists of more than 8000 members. About 4000 members are doctors from various specialties, 3500 are nursing staffs and about 500 are other personnel such as case workers and pharmacists. The Japan Nursing Association established an integrated training course for nurses majoring in palliative care and qualifying through examinations in 1996 and 1997 (4). They are Certified Nurse Specialist for Cancer Nursing (CNSCN) and Certified Nurse in Palliative Medicine (CNPM). In 2009, about 80 CNSCNs and 680 CNPMs were working as palliative care experts in Japan. The MHLW introduced reimbursement in health insurance for palliative cancer care team at each specially certified hospital in 2002. In 2006, the Cancer Control Act was passed by the Congress and a basic plan to promote the Cancer Control Program (CCP) was drawn up in the Cabinet and sent to the MHLW (5,6). Under this CCP, a plan to promote CCP has established in each prefecture. The Ministry of Education, Culture, Sports, Science and Technology (MECSST), Japan, has promoted 18 consortiums of graduate universities for a plan to expand integrated and standard cancer care all over Japan from 2007. However, only about 30 doctors majored in the course of palliative medicine in the first year, and 1/10th of those chose the courses of cancer chemotherapy and therapeutic radiology. In 2008, the Japanese Society for Pharmaceutical Palliative Care and Sciences established a qualification system of pharmacists specialized in pharmaceutical palliative cancer care. In 2009, the NPO-JSPM established a qualification system for expert doctors in palliative medicine. Twelve specialists have been certified out of a hundred applicants for the paper, through oral examinations, from all over Japan (3).

ADVANCES OF QUALITY OF PALLIATIVE MEDICINE: SKILLS AND DRUGS

Various new drugs and interventions have been introduced during the past 15 years in the area of palliative medicine in cancer. In 1996, a special issue for palliative cancer care was published in the Journal of the Japanese Society of Internal Medicine (7). The contents consisted of informed consent, breaking bad news, communication skill, euthanasia and withholding or withdrawing medical treatment, terminal care at home and starting palliative care team at the hospital. These issues are still fundamental and important aims for high-quality practice and are major educational topics both for doctors and other medical staff in palliative medicine for
cancer patients. However, the recommendations for symptoms control was restricted to the use of a few conventional drugs. Since then, innovative drugs and methods have changed clinical practice dramatically in palliative medicine.

Currently, a doctor can choose each opioid for pain control depending on the patient’s condition and the spectrum of risk/benefit of a formula (8). Besides the conventional slow-releasing type morphine, transdermal fentanyl patch was approved in 2001 and oral oxycodone hydrochloride in 2003. Fentanyl is a semi-synthetic opioid and is not used orally because of rapid extensive first-pass metabolism. Fentanyl seems to cause less constipation and nausea than the other opioids. Oxycodone hydrochloride is a semi-synthetic opioid and has agonist action at µ- and κ-receptors. Oxycodone, when used orally, is 1.5 times as effective as morphine. It can be used in patients with renal and hepatic impairment. Compliance with the use of opioids for cancer pain control improved with choosing the ‘opioid rotation’ method such as switching to another opioid and/or applying another route of administration.

Neuropathic pain is difficult to lessen with opioids alone. Various other pharmacological agents, such as anticonvulsant gabapentin, N-methyl-D-aspartate antagonist ketamine etc., should use concurrently. New antidepressants such as selective serotonin reuptake inhibitor, paroxetine, and serotonin noradrenaline reuptake inhibitor, milnacipran, can be effective against persistent neuropathic pain with concomitant use of opioids under the advice of psycho-oncologist. However, in Japan, the use of most of these neuropharmacological agents is not approved for cancer pain and not covered by health insurance for the palliative care setting.

In the case of chemotherapy-induced neutropenia, recombinant human granulocyte colony-stimulating factors were approved in the mid-1990s and used under the guidelines of the oncology society. In Japan, both 5HT3 receptor antagonists (in mid-1990s) and neurokinin one receptor (NK-1R) antagonist (in 2009) were approved for use as the antiemetics for chemotherapy-induced nausea and vomiting, in addition to the classic antiemetic dexamethasone. However, there is lack of evidence on the effectiveness of these new agents for opioid-induced nausea and vomiting in advanced cancer patients. The low response of these new drugs may be partly explained by the difference of mechanism of action between chemo- and opioid-induced nausea and vomiting. Besides, corticosteroids dopamine D2 receptor antagonists such as metoclopramide and haloperidol have been shown to be effective for nausea and vomiting in patients with far advanced cancer (9).

Octreotide was developed to reduce nausea and vomiting from malignant bowel obstruction and was approved in Japan in 2004. For malignant hypercalcemia, third generations of bisphosphonates have been developed. For decreasing malignant bone-related events such as pathological fracture and improving survival, new bisphosphonate zoledronate was approved in 2005. Zoledronate is effective in decreasing the frequency of pathological bone fracture and slowing down of the progression of bone metastasis through depressing the activity of osteoclast (10). Radionuclides that are absorbed at bony foci with high turnover are applied to potential therapy for bone pain due to multiple metastases. In Japan, radioisotope Sr-89 (Metastrone) was approved in 2007 to reduce persistent cancer pain with multiple bone metastases in palliation for a few months (11). For severe pain due to metastasis to vertebra, the injection technique of bone cement was developed as a new radiological intervention and a multicenter Phase II trial is on-going in Japan.

As shown in the brief paragraph on ‘drug lag’, a delayed procedure of approval by the MHLW is still an important problem in the area of palliative care.

The concept of practice in palliative cancer care has rapidly and dramatically changed in the early 2000s mainly because of two major advances in clinical oncology. Reimbursement of health insurance for chemotherapy in the outpatient setting started at certified hospitals in 2002 and clinics in 2004. The number of cancer patients who received chemotherapy for months and years without staying in hospital has rapidly increased in Japan. Many patients can spend their lives at home, receiving treatment in an outpatient setting. New molecular-targeted drugs have been rapidly introduced to clinical oncology as major advance of palliative chemotherapy, improving performance status and achieving long-term remission. There are many new small molecules with oral administration such as imatinib mesylate for Phi-positive chronic myeloid leukemia and CD117-positive gastrointestinal stromal tumor, the epidermal growth factor receptor (EGFR)-thyrosine kinase inhibitors gefitinib and erlotinib for non-small cell lung cancer with mutation of EGFR-positive (12). Performance status and QOL of advanced cancer patients suffering from the corresponding tumors to these effective drugs improved dramatically. Appropriate molecular indicators will be established for the selection of better target population of patients. By adequately combining these treatments, some patients even with far advanced cancer can spend their daily lives at home for months and years. Patients and their families want to choose palliative care in an outpatient setting and want to choose staying at hospital only in an emergency setting. The ‘tailor-made’ approach of cancer treatment using molecular markers brought about paradigm shift of palliative care, from the viewpoint of care and patients’ style of daily life. However, new molecular-targeted drugs result in various expected and unexpected adverse effects. Clinical research and trials for establishing effective supportive care for these adverse effects will be mandatory in palliative medicine.

CURRENT ISSUES TO OVERCOME IN JAPAN

How can patients receive integrated high-quality cancer care wherever they are in Japan? Unfortunately, there are various obstacles to fulfilling patients’ and their families’ hopes because of the heterogeneity of various geographical, social and medical backgrounds among the various districts.
According to the vital statistics reported by the MHLW, the age-adjusted death rate in Aomori Prefecture (104 per 100,000 person) was 1.4 times that of Nagano Prefecture (76 per 100,000 person) in 2007 (13). In 2008, there were only four prefectures that had more than 20 beds (for hospice care) per 1000 cancer deaths in Japan. Totally, there are 4060 beds for hospice care and about 360 approved hospices by the MHLW in Japan in 2010. However, only 59 out of 377 approved oncology hospitals (16%) have a specially equipped ward for palliative care. Among these approved oncology hospitals, only 90 out of 377 (24%) have a palliative care team (14).

The Japan Hospice Palliative Care Foundation performed a survey using questionnaires for the general public about home care for the terminally ill in 2007 (15). About 900 people responded. More than 80% of responders wanted to receive care at home; however, about 60% of people thought it would be impossible because of burdens for care givers, lack of information regarding preparing for emergency situations, etc. It is mandatory to enlighten people’s perception of palliative home care and expand resources of medical and nursing care services. The questionnaires for Japanese doctors who engaged in clinical practice for cancer medicine have been conducted by a task-force team of the Japan Medical Association in 2008 (16). About 46,000 doctors corresponded and it was the largest survey on doctors’ perception for palliative cancer care in Japan. Doctors recognized well the importance of general aspects of palliative cancer care, but could not answer more specific questionnaires on skill and knowledge of palliative medicine. Education and training for medical and nursing staff will be mandatory for improvement and to overcome these issues. Whole aspects of better life for patients and family in each community are shown in Fig. 1. The CCP declares that they should easily be able to find and reach various kinds of support and better management in every district of Japan within 5 years.

THE OUTREACH PALLIATIVE CARE TRIAL OF INTEGRATED REGIONAL MODEL STUDY IN JAPAN

The Outreach Palliative care Trial of Integrated regional Model (OPITM) study, supported by the MHLW, is a strategic interventional trial for 5 years to develop procedures and systems of community-scale palliative cancer medicine for patients and their families (17,18). The aim of the program includes (i) early intervention of palliative care for patients suffering advanced cancer and their families, and (ii) effective cooperation of various support staff, at the hospital, clinic, nursing center, pharmacy, home welfare services etc., in the area where patients spend their daily life. Four municipalities were selected as experimental fields, that is, an area with and without a network of activity in palliative care. In the ‘with’ areas, there are three types of core institute, such as a large general hospital, a medical association in a district and a center institute specialized for cancer medicine. The OPITM study is not a randomized controlled trial and applies a pre- and post-comparative design. It is to assess the efficacy of integrated intervention and organized network with human resources, tools and specific facilities. In the OPTIM study, the primary endpoint consists of QOL scores rated by patients and families, the frequency of use of specific palliative care services and the death rate at home, and the final report will be published in 2013. If our

Figure 1. Network for community supported cancer care.
intervention study results in real improvement of the primary endpoint, we will recommend to the MHLW, a plan to conduct the system of palliative cancer care in each community of Japan under the guidance of procedures suggested in the OPTIM reports.

ENLIGHTENMENT AND EDUCATION OF PALLIATIVE CARE IN CANCER PATIENTS

Various educational events have been conducted for lay people by several societies, related to palliative care in Japan. Recently, patients’ advocates have also been actively involved in these movements, cooperating with medical and nursing societies. Systematic educational programs for primary medical staff and special projects for training leaders and experts in palliative medicine are conducted by the above-mentioned societies (Fig. 2). Those are partly supported by the MHLW, such as the ‘Orange balloon project’ for lay people. The NPO-JSPM is conducting the PEACE (Palliative care Emphasis program on symptom management and Assessment for Continuous medical Education) project for trainers and regular seminars for medical students and for primary staff in cancer medicine using integrated curricula with the support of the MHLW (3). In 2009, about 10,000 doctors completed integrated educational courses such as the PEACE projects. The MECSST supports projects conducted by consortiums of graduate schools of medicine, such as Gan (Cancer) professional training course (19).

Currently, there are only few chairs and courses for palliative medicine in universities and medical colleges in Japan. A major breakthrough will be sure to increase the number of courses and chairs for palliative medicine in most of the universities and medical colleges in Japan.

Continuous educational programs of primary palliative medicine for clinicians will be important and will urgently to be maintained by the cooperation of the trainers who graduate from the PEACE project. The JSPM will make efforts to increase the number of certified specialists for palliative medicine to a minimum of 2000 doctors within several years, expecting that each core hospital in a district should have two to three certified experts. These specialists will be anticipated to work in specific consultation cooperating with nursing specialists on active triages of patients in the community.

All medical staff should be aware of the importance and essence of palliative care in cancer medicine. We will continue our efforts to offer high-quality palliative care to improve and keep better QOL of cancer patients and their families.

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Conflict of interest statement

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