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The Groningen Protocol – No Ordinary Protocol

Dr. Doris TSE Man-wah, Editor-in-Chief

The Groningen Protocol is not any ordinary clinical protocol. It is a protocol named after the Groningen University Medical Centre, where this protocol was drafted by a group of doctors for euthanasia of infants. Although regarded as a “newly” published guideline in 2004, infanticide is not new in Netherlands. In Groningen University Medical Centre, the guideline was followed when killing 22 disabled newborns between 1997 and 2004. In the Groningen Protocol, euthanizable babies are categorized into infants “with no chance of survival,” infants with a “poor prognosis and dependent on intensive care,” and “infants with a hopeless prognosis”, including those not depending on intensive care. In other words, the protocol is not just about killing babies who would otherwise be dying, but babies who are predicted to be "hopeless." As these babies cannot defend themselves and cannot exercise or express their free will, the Groningen Protocol is dependent on the subjective judgment by parents and doctors of the baby that he or she is suffering hopelessly and unbearably, and that his or her quality of life is very poor. Premature babies with brain damage, severe cases of spina bifida are examples that fall into these categories.

This Groningen Protocol for the babies could well extend to others who cannot express their will to live in Netherlands, such as those who are mentally retarded or demented. In Netherlands, adolescents and children are accessible to physician assisted suicide since the 1980’s. The age of consent for euthanasia has been reduced to 12-years-old, and can occur without consent of their parents.

The Royal Dutch Medical Association, after 3 years of inquiry, issued a report saying that doctors can help patients who ask for help to die even though they may not be ill but “suffering through living”. (BMJ 2005;330:61) This report contradicts a landmark Supreme Court decision in 2002 that a patient must have a “classifiable physical or mental condition.” In that landmark case, a GP was found guilty of helping his 86-year-old patient die - one who had no medical illness, but overwhelmed by his physical decline and hopeless existence. (BMJ 2003;326:71).

If you are not aware that euthanasia has gone that far since it was legalized in Netherlands in early 2000’s, you may be astonished to find out that euthanasia is no longer limited to the sick who strongly and persistently request so, but including infants who still have to learn to speak and those who find living not bearable not because of illness.

In response to all these movements in Netherlands, the debate goes on. “We do not value life on a sliding scale. All are equal,” said Bob Barr, a former Republican member of the U.S. House of Representatives from Georgia. Wesley J Smith, an attorney for the International Task Force on Euthanasia and Assisted Suicide, expressed his immense concern: “The slippery slope in the Netherlands has descended already into a vertical cliff.”

The year of 2006 ended with some more related news. Jack Kevorkian, trained as a pathologist, and also well known as Dr. Death, will soon be out of jail on parole. He was found guilty of helping his 86-year-old patient before Christmas 2006, after a doctor disconnected his respirator.

Piergiorgio Welby, 60, who suffered from degenerative muscular dystrophy, wrote to Italian President Giorgio Napolitano to appeal for euthanasia. He died five days before Christmas 2006, after a doctor disconnected his respirator.

From respecting sanctity of life to classifying a life less worth living than the other, From believing in almighty high technology medicine to concluding therapeutic nihilism, Where are we humans, as spiritual beings, heading for?
Death and dying affect more than an individual, and should be considered a family event. Epidemiologically, each year at least 150,000 to 200,000 persons in Hong Kong are affected by death events, assuming a dying person affects 3 to 4 persons on average.

Locally, there have been many discussions on “ageing in place”, but little discussion has been focused on “dying in place”. A survey conducted by the Society for the Promotion of Hospice Care on “Good Death” in 738 subjects sampled from the public in 2004 showed that “dying at home” scored the lowest among 14 items (2.72 out of score from 1 to 10). Another survey conducted by SPHC in 430 subjects among public in 2002 showed that 27.2% preferred dying at home if they were terminally ill. (Table 1) No formal study has been conducted on “Good Death” among the terminally ill in Hong Kong. Nevertheless, responses from the residents of Haven of Hope Nursing Home did show a rising trend and significant proportions (30% of all deaths of nursing home from April 2005 to March 2005) of terminally ill residents had shown a preference of “dying in place” in nursing home (Dr W Chu, personal communication). Factors affecting place of death including patient and family factors, care factors and system factors.

For seniors who moved to a nursing home, albeit the support gained from the care of nursing home, the psychological journey of the family is often a process of saying goodbye to one after the other: to health and independence, to home environment and family, to the state of full recovery and finally to life itself. The seniors and family have to face a new form of relationship in terms of accepting the nursing home as a “surrogate home” and nursing staff as “surrogate caregivers”. To prepare for the smooth transition, certain degree of transfer of responsibility from family to nursing home staff and the formation of trusting relationship between the family and staff of nursing home should occur. The story of my father was shared as an illustration for this journey. He suffered from normal pressure hydrocephalus with progressive mobility impairment and mental decline over two decades. He was admitted into Haven of Hope Nursing Home at late 1999.

The recognition of the progressive losses and the preparation for the anticipatory grief for our loved one with progressive disease are especially important for family during this journey. Planned living in the dual perspectives of present and future is especially helpful. Delivery of tangible care, fulfillment of wishes, communication, being present, life review and reflective writing by family members are possible ways to recapitulate and reorganize relationship with the senior. Reflective writing has become my way to express my personal anticipatory loss. Through reflective writing, I recapitulated past events, reorganized my inner world, expressed emotions, grieved future losses and captured past memories as legacy. Organizing parents’ photo album was taken up by my sister as a mean to address the anticipatory loss. These photos had helped in capturing past memorable moments, organized events, facilitated emotional expressions and integrated relationship internally.

Nevertheless, the most difficult issue concerning last days is to bring about open discussion about it within the family. This process takes courage, sensitivity, opportunity and skill for initiation and conduction, and the realization that dying is a natural process in life. Most seniors are comfortable to discuss about this in the context of advanced life planning. Although issues related to treatment decision such as prolonging life versus quality of life could be a struggle, attitudes towards death and dying, family dynamics and communication will shape the final process.

My elder brother timely returned to Hong Kong to see my father after his health had deteriorated considerably. We decided to let our father stayed in nursing home. He passed way peacefully at one midnight without any distress. No CPR was conducted. His last office was assisted by me. My family said goodbye to him in the room behind the chapel where his body stayed. A memorial album was printed to capture all our memories to our Dad.
A substituted home environment, with the care provided by the formal caregivers of nursing home who are skilled at end-of-life, can therefore be a place of peaceful death for the senior. Elders with diseases of progressive course and predictable prognosis are suitable candidates. Within this home, there are minimal institutional barriers and minimal over-enthusiastic medical interventions during the last phase of life. The psychological preparation of the family is important for a peaceful death.

Local barriers of dying in nursing home should be addressed so that peaceful death can be achieved for selected person who requires minimal medical interventions and whose life will end predictably.

Reference

Table 1.
Survey on preference of place of death among public conducted by SPHC in 2002, n=430

<table>
<thead>
<tr>
<th>Place</th>
<th>Total %, (n)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>At home</td>
<td>27.2 (117)</td>
<td>29.3 (54)</td>
<td>29.6 (63)</td>
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<tr>
<td>Hospital/nursing home</td>
<td>37.0 (159)</td>
<td>32.6 (60)</td>
<td>40.2 (99)</td>
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<tr>
<td>Others</td>
<td>3.5 (15)</td>
<td>3.3 (6)</td>
<td>3.7 (9)</td>
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<tr>
<td>Don't know</td>
<td>30.5 (131)</td>
<td>32.1 (59)</td>
<td>29.3 (72)</td>
</tr>
<tr>
<td>Refused to answer</td>
<td>1.9 (8)</td>
<td>2.7 (5)</td>
<td>1.2 (3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100.0 (430)</strong></td>
<td><strong>100.0 (184)</strong></td>
<td><strong>100.0 (246)</strong></td>
</tr>
</tbody>
</table>
Recent Advances in Management of Symptoms Other Than Pain in Palliative Care

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After more than two decades of palliative care in Hong Kong, one of the challenges ahead is to have practices based on more research into pathogenesis and new therapeutics for refractory symptoms, existential and spiritual distress, and bereavement. In the following review, recent articles published between 2003 and 2006 of randomised controlled trials (RCT) and clinical trials which represented significant advances or would create an impact on the field of palliative medicine are selected and presented.

Cachexia

The cancer cachexia syndrome has been postulated to be due to persistent inflammatory response by the host producing inflammatory cytokines (e.g. TNF-α, IL1-β, INF-γ, IL-6) and tumour-specific catabolic factors produced by the tumour (e.g. PIF, LMF).1 A number of agents have been used to treat cancer cachexia including steroids, progestogens (megestrol acetate and medroxyprogesterone), non-steroidal anti-inflammatory agents, cannabinoids, eicosapentaenoic acid, fish oils, and pentoxyfylline. Only megestrol acetate has been confirmed by large-scale systematic reviews to improve appetite, weight gain, and possibly quality of life in cancer patients.2, 3

Thalidomide, an inhibitor of tumour-necrosis factor-α, has been shown in a double-blind RCT to attenuate loss of weight and lean body mass in patients with advanced pancreatic cancer.4 Thalidomide 200 mg or placebo was given daily to 50 patients with over 10% loss of body weight in the past six-months. At 4 weeks, patients taking thalidomide had a mean weight gain 0.37 kg while those on placebo lost 2.21 kg on average (p=0.005). The arm muscle mass increased by a mean of 1.0 cm³ in the thalidomide group while it decreased by a mean of 4.6 cm³ in the placebo group. (p=0.002). This significant improvement was also shown at 8 weeks post-treatment. The drug was well tolerated.

Fatigue

A double-blind RCT comparing patient-controlled Methylphenidate (5 mg every 2 hours as needed) with placebo in 112 cancer patients with moderate to severe fatigue (fatigue score of at least 4 in a scale of 0-10) showed a significant improvement in fatigue score and other symptoms as assessed by Edmonton Symptom Assessment Score (ESAS) in both groups, but no significant difference between the treatment and the placebo groups. The improvement achieved in both groups was postulated to be possibly related to the daily phone contact by the research nurse. No significant toxicity was observed.5

Dyspnoea

A locally relevant assessment tool, the Quality-of-life Concerns in the End-of-life, has been developed and validated by a collaborative effort of three hospitals for patients with advanced chronic obstructive pulmonary disease (COPD) and cancer.6

Oxygen supplement had been shown to be superior to air in a double-blind study by Bruera in 1993 to relieve dyspnoea in hypoxic terminal cancer patients. However, for advanced cancer patients without hypoxia who had moderate to severe dyspnoea, a double-blind crossover RCT comparing 5L oxygen versus air failed to show a significant improvement in dyspnoea, fatigue and distance walked.7

From a systematic review, systemic opioids were shown to improve sense of breathlessness while nebulized opioids did not.8 In a randomized, double-blind, placebo controlled crossover trial of predominantly COPD patients comparing 20 mg of sustained release morphine and placebo, participants reported significant improvement in dyspnoea scores when treated with morphine: an improvement of 6.6 mm on a 100 mm visual analogue scale (95% confidence interval 1.6-11.6 mm) in the morning (p=0.011) and of 9.5 mm (95% CI 3.0-16.1 mm) in the evening (p=0.006). No excessive sedation or respiratory depression was observed in the morphine group.9
On the other hand, with the potential advantages of a more rapid onset, ease of administration both at home and in hospital, and fewer systemic side effects, researchers looked into the use of nebulized morphine again. In a recent double-blind, placebo controlled crossover RCT in 15 advanced cancer patients with resting dyspnoea directly comparing nebulised and subcutaneous morphine, there was a significant improvement in median dyspnoea score in both groups at 30 minutes and 60 minutes after administration (subcutaneous morphine group: median dyspnoea score at time 0=5 out of a numerical scale of 0-10; at 30 minutes=3, p=0.005; at 60 minutes=3, p=0.025; nebulized morphine group: median dyspnoea score at time 0=4; at 30 minutes=2, p=0.011; at 60 minutes=2, p=0.007) and the effect lasted for several hours. However, there was no significant difference in reduction of median dyspnoea score between the groups.

This study is limited by its small sample size, and a larger randomized trial is called for to explore and delineate the role of nebulized morphine in dyspnoea management.

Other treatments that have been investigated in dyspnoea management included midazolam, nebulized furosemide and acupuncture. A RCT from Argentina showed that adding midazolam as an adjunct to morphine reduced resting dyspnoea in end-of-life. Nebulized furosemide, which was postulated to act by blocking chloride channels in airways and reducing bronchospasm, had been shown in an open trial by a Japanese group to reduce dyspnoea especially regarding sense of effort in breathing and associated anxiety, and further prospective trials are called for. A single-blind, randomized crossover trial comparing TENS (transcutaneous electrical nerve stimulation) and a standardised acupuncture technique showed a significant improvement in dyspnoea in patients with chronic lung diseases, predominantly COPD, in both groups.

**Delirium**

Pharmacological treatment of delirium classically involves use of haloperidol, sedative neuroleptics like chlorpromazine, and newer neuroleptics like risperidone and olanzapine, though randomised controlled trials are lacking. The only prospective trial included in a 2004 Cochrane review dated back to 1996. It involved 30 hospitalized AIDS patients, and it showed that haloperidol and chlorpromazine were equally effective but more cognitive impairment resulted from chlorpromazine.

Methylphenidate, a psychostimulant acting on the reticular activation system, had been prospectively tested in 14 advanced cancer patients suffering from hypoactive delirium. It resulted in improvement in cognitive function (reflected by Mini-Mental State Examination Score), alertness, psychomotor retardation, slurred speech and energy level. The result has yet to be confirmed by controlled trial.

**Terminal Care**

In a Hong Kong study, fatigue, cachexia, and anorexia were found to be the most distressing symptoms in the last week of life. However caregivers and physicians tended to underestimate the prevalence and the level of distress the patients were experiencing. With the current difficulty in treating these ‘negative’ symptoms, palliative care workers can still acknowledge such symptoms at the end-of-life and attend to details proactively.

Artificial hydration has long been a controversial issue in palliative care. Bruera conducted a double-blind RCT in 51 advanced cancer patients with clinical or biochemical evidence of mild to moderate dehydration plus a daily oral fluid intake below 1 litre, comparing parenteral hydration of 1000 mL per day versus placebo (giving 100 mL instead). Myoclonus and sedation improved significantly in the hydration group while hallucinations and fatigue showed no significant improvement.

For intractable distress at life’s end, anaesthetic agents like dexmedetomidine (α-2 agonist) and propofol had been tried for palliative sedation with the target of achieving a state of ‘conscious sedation’ and are reported to be useful in small case series. Further trials are warranted.

**Spiritual distress**

Different researchers around the world have been trying hard to define the spiritual dimension in palliative care, and to develop management tools based on the theoretical model defined. Some of the models and their researchers were listed in Table 1. Kissane’s demoralization model attempted to differentiate from clinical depression an entity comprising of hopelessness, meaninglessness, purposelessness, and helplessness and a 24-item demoralization scale had been validated. Based on Victor Frankl's meaning-based therapy, Breitbart devised an 8-week group psychotherapy sessions to help patients with advanced cancer to sustain or
enhance a sense of meaning, peace and purpose. With positive outcomes from a pilot study, a randomized controlled trial was underway. Chochinov had formulated the Dignity-Model and Dignity Psychotherapy Question Protocol as diagnostic tools to explore aspects of life that patients considered most important, meaningful, worthy to be remembered and to be left behind. A therapeutic tool, Dignity Therapy, which involved one to two sessions lasting not more than one hour that could be done at patients’ bedside, with a tangible end-product in the form of a ‘generativity document’ to be given to the their loved ones, had been tested in 100 patients showing improvement in suffering measures and depressive symptoms. An international RCT was in progress.

**General Issues**

In a pilot study involving 34 incurable cancer patients with life expectancy of 3-12 months, a six-week exercise program was reported to lead to improvement in physical ability, emotional/social/role functioning, physical fatigue and dyspnoea. Other therapies that have been reported by prospective studies to alleviate symptoms and distress include art therapy and aromatherapy.

**Complicated Grief**

Routine intervention for normal bereavement has not been shown by review of studies to be effective in facilitating adjustment to loss. Attention should be paid more to the group with complicated grief. Complicated grief comprises of sense of disbelief regarding the death, anger and bitterness over the death, recurrent pangs of painful emotions with intense yearning and longing for the deceased, preoccupation with thoughts of the loved ones, and avoidance behaviour for situations that act as reminders of the loss. The prevalence is around 10-20 % of bereaved people. Proposed criteria for complicated grief definition in DSM-V is under review.

A prospective RCT involving 95 bereaved diagnosed to have complicated grief compared a sixteen-week specific Complicated Grief Treatment with Interpersonal Psychotherapy. The Complicated Grief Therapy involved loss-focus interventions addressing trauma-like symptoms using procedures for retelling the story of the death (revisiting) and exercises entailing confrontation with avoided situations, and restoration-focus interventions defining personal goals and formulating concrete plans. It led to better and earlier improvement in complicated grief symptoms than Interpersonal Psychotherapy.

**Conclusion**

This review attempts to capture some of the recent advances in palliative care besides pain control. In the twenty-first century, we need a solid base of knowledge based on research with appropriate design, bearing in mind the specific difficulties in performing research in this group of vulnerable patients who are in great need of competent and compassionate care.
Reference


Recent Advances in Cancer Pain Management

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This article will focus on:
1. Guidelines and recommendation on opioid treatment of cancer pain;
2. Recent evidences in comparing morphine and methadone as first line opioid, management of breakthrough pain, pharmacological treatment of neuropathic pain and use of bisphosphonate in cancer related bone pain.

Guidelines and recommendation on opioid treatment of cancer pain

The Expert Working Group of the Research Network of the European Association for Palliative Care (EAPC) has published guidelines and recommendation on use of morphine and alternative opioids in cancer pain in 2001. The following are the salient points:

1. Morphine is the first choice of strong opioid for moderate to severe pain
2. The optimal route of administration of morphine is by mouth;
3. The dose for breakthrough pain is suggested to be the same dose as regular 4-hourly immediate release morphine;
4. Methadone is an effective alternative but it have pronounced inter-individual differences in its plasma half life ranges from 17 to 100 hrs, relative analgesic potency and duration of action; and
5. Transdermal fentanyl is an effective alternative but is best reserved for patients whose opioid requirement is stable.

Recent evidence in comparing Morphine and Methadone as first line opioid

A randomized, double-blinded study in 2004 comparing methadone with morphine as a first line strong opioid for cancer pain found that methadone did not produce superior analgesic effect or overall tolerability at 4 weeks compared with morphine as a first line strong opioid. Both methadone and morphine groups reported that 70% of patients had more than 20% improvement in pain at 4 weeks. However there was a significant higher drop out rate in methadone group compared to the morphine group (22% Vs 6%, p =0.019).

Recent evidence in management of breakthrough pain

Breakthrough pain is also described as episodic pain, transient pain and pain flare. It is characterized by transient increase in pain intensity over background pain. It is usually rapid onset, severe in intensity and self limiting.

EAPC has recommended using immediate release oral morphine of dosage around 16% of total daily dose for breakthrough pain. The rescue dose can be given as often as required up to every 1-2 hr orally and up to 15-30min intravenously.

A recent systematic review on use of opioids for management of breakthrough pain in cancer patients in 2005 has included four randomized control studies involving a total 393 of participants, studying the efficacy of transmucosal fentanyl citrate (OTFC) compared to placebo and morphine. OTFC consists of a fentanyl impregnated sweetened and hardened lozenge on a plastic handle and designed for breakthrough pain. It has a very rapid onset of action, ranging from 5-15 min, and has a short duration of action of around 2 hrs. This review found that OTFC was superior to placebo, immediate release morphine and previous rescue medication in providing breakthrough pain relief at 15min and 30min. They also found that the successful dose of OTFC was determined by titration and there was no relationship between the successful dose of OTFC and the total daily around the clock opioid. The practice of deliver a fixed proportion of the around the clock dose for breakthrough pain medication as recommended by EAPC is not supported by this review.
Recent evidence in pharmacological treatment of neuropathic pain

**Antidepressant**

The use of antidepressant in non-malignant neuropathic pain has been extensively studied. A recent review of 50 trials including 2515 patients found that amitriptyline up to 150mg daily had an number need to treat (NNT) of 2. Evidence also suggests that other tricyclic antidepressants are effective, but the number of patients are insufficient to calculate NNT. Adverse events of tricyclic antidepressant include drowsiness, dizziness, dry mouth, constipation, nausea, urinary retention, sweating, headache, blurred vision, palpitations, irritability and ataxia. Newer generation of antidepressants including the selective serotonin reuptake inhibitors (SSRIs) and the mixed serotonin-noradrenaline reuptake inhibitors (SNRIs) have also been adequately tested in nonmalignant neuropathic pain. For SSRIs, the overall NNT is nearly 7 and for SNRIs the NNT is 4.1-5.5. Both do not appear to be as effective as amitriptyline in neuropathic pain. However, there are only few clinical trials which have specifically evaluated the use of antidepressant for cancer pain, and results are controversial.

**Anticonvulsant**

Carbamazepine is the most widely studied drug for neuropathic pain, especially trigeminal neuralgia. In a systematic review of 12 randomized trials with 404 patients, carbamazepine has a NNT of 2.5 for any neuropathic pain. Adverse effects include drowsiness, dizziness, constipation, nausea and ataxia. There are only very limited studies on the use of carbamazepine in cancer related neuropathic pain. For SSRIs, the overall NNT is nearly 7 and for SNRIs the NNT is 4.1-5.5. Both do not appear to be as effective as amitriptyline in neuropathic pain. However, there are only few clinical trials which have specifically evaluated the use of antidepressant for cancer pain, and results are controversial.

**Opioids**

A Cochrane review of 14 short term studies (less than 24 hours) found that efficacy of opioids in reducing intensity of neuropathic pain was only equivocal. However a review of 9 intermediate-term studies (median 28 days, ranged from 8-70 days), showed that its efficacy was significantly better than placebo with mean visual analogue scale (VAS) 13 points lower on the scale, p<0.00001. Tramadol is a weak mu-opioid receptor agonist and a mixed serotonin and noradrenaline reuptake inhibitor. It belongs to the second ladder of the World Health Organization (WHO) scale. It has high oral bioavailability and is widely metabolized in liver. Its main metabolite M1 is pharmacologically active. Dosage adjustments are required with renal or liver failure. Because of the dual activity (opioid and monoaminergic activity), use of tramadol in neuropathic pain has been widely studied. A systematic review of 3 trials comparing tramadol with placebo showed a significant reduction in neuropathic pain with tramadol with NNT 3.5 to reach at least 50% pain relief. Common side effects reported were nausea, vomiting, sweating, dry mouth, dizziness and sedation.
Methadone is a potent agonist at mu-opioid and delta-opioid receptors. Besides, it also has N-methyl-D-aspartate (NMDA) receptor antagonist activity. However, there are no trial evidence to support the postulation that methadone has a particular role in neuropathic pain of malignant origin\(^\text{18}\). Concerning other NMDA receptor antagonists such as ketamine, current evidence is insufficient to assess the benefits and harms in neuropathic pain management due to limited randomized control trials\(^\text{19}\).

**Recent evidence in use of bisphosphonate in cancer related bone pain**

**Background**

Bisphosphonates are structure analogues of pyrophosphates, a naturally occurring component of bone crystal deposition. Different side chain modifications of the basic pyrophosphate structure give rise to different generations of bisphosphonates with different level of activity. They prevent bone loss by binding to active sites of bone remodeling, inhibiting osteoclast-mediated bone resorption and eventually causing osteoclast apoptosis. There are different generations of bisphosphonates:

1. **Clodronate**, which is available in both oral and intravenous form, but the oral form is limited by its gastrointestinal side effect.
2. **Palmidronate**, which is available in intravenous form and suggested dosage ranged from 60-90mg infused over 2 hours every 3-4 weeks.
3. **Zoledronic acid** which is available in intravenous form with suggested dosage of 4-8mg infused over 15 min every 3-4 weeks.
4. **Ibandronate** which is the newest generation of bisphosphonates available in both oral and intravenous forms with suggested dosage of 50mg daily orally or 6mg infused over 1hr every 3-4 weeks intravenously.

**Efficacy of zoledronic acid in prevention of skeletal related event**

A review of three randomized double-blind multicenter trials which assessed the efficacy of zoledronic acids (4mg) infused over 15 minutes found that zoledronic acid showed evidence of reduction in skeletal related events in breast cancer, multiple myeloma, prostate cancer, lung cancer and other solid tumor. In contrast, previous generation of bisphosphonate (clodronate and palmidronate) only showed efficacy in breast cancer and multiple myeloma. Skeletal related event was defined as pathological fracture, spinal cord compression, radiation therapy to bone, and surgery to bone\(^\text{20}\).

**Efficacy of zoledronic acid in reduction of bone pain**

Comparing zoledronic acid with placebo, there was significant difference in pain score in patients with breast cancer and bone metastasis (p=0.0004). However when comparing zoledronic acid with palmidronate, there was no significant difference. In clinical trials on patients with bone metastasis from other tumors, zoledronic acid had no significant effects on bone pain, quality of life and performance status\(^\text{20}\).

**Effect of zoledronic acid on renal function**

A total of 72 cases of renal dysfunction associated with zoledronic acid were identified in the US Food and Drug Administration (FDA) Adverse Event Reporting System from August, 2001 to March, 2003. Of the 72 patients, 27 patients required dialysis and 18 died. The underlying risk factors for renal deterioration in these patients included advanced cancer, previous bisphosphonate exposure and concomittent use of NSAID\(^\text{21}\). The product label was updated to include additional warning of nephrotoxicity and restrictions for patient with varying degrees of renal impairment.

**Efficacy of ibandronate in prevention of skeletal related event**

The efficacy of intravenously and orally administered ibandronate has been assessed in three randomized, double-blind, placebo controlled studies. Intravenously administered ibandronate (6mg over 1-2 hours) and orally administered ibandronate (50mg daily), significantly decreased skeletal morbidity period rate (p=0.004) and risk of skeletal related event (40% and 38%, p =0.003 and p<0.001 respectively) in patients with breast cancer and bone metastasis. Skeletal morbidity period rate was defined as the number of 12-week periods with skeletal complications (vertebral fractures, non-vertebral fractures, radiotherapy to bone and surgery to bone) divided by the total observational time\(^\text{22-23}\). Another small trial on 15 patients with colorectal cancer metastasis to bone found that patients treated with intravenous ibandronate had significantly less skeletal related events compared with placebo (39% Vs 78%, p =0.019)\(^\text{24}\).
Efficacy of Ibandronate in reduction of bone pain

Both intravenously and orally administered ibandronate had been shown to reduce bone pain score significantly better than placebo (p < 0.001) in breast cancer patients with bone metastasis 25,26. More recently, studies have demonstrated that intensive ibandronate dosing provided rapid and effective relief from moderate to severe metastatic bone pain. In an open labelled trial of 18 patients with opioid resistant bone pain due to various primary tumours, high doses of intravenous administered ibandronate (4mg x 4 consecutive days) led to significant reduction in bone pain scores within 7 days (p<0.001) and the pain reduction effect was maintained for 6 weeks27. In another trial on 53 metastatic urologic cancer patients with bone pain and hypercalcemia, bone pain scores improved in 83% of patients (mean score p<0.001 versus baseline on day 3), with 25% of patients becoming pain-free28.

Effect of Ibandronate on renal function

Results from clinical studies have demonstrated that ibandronate has a renal safety profile comparable with placebo. Dosage adjustment is not required in mild to moderate renal impairment and renal function monitoring is not mandatory at physician’s direction20.

American Society of Clinical Oncology (ASCO) guideline on the role of bisphosphonate in cancer patients

The American Society of Clinical Oncology (ASCO) recommended intravenous bisphosphonate every 3-4 weeks in patients with breast cancer and multiple myeloma with lytic lesions on plain radiograph to reduce skeletal complication. However there is no consensus on whether it should be started in other tumours to prevent skeletal complication. ASCO has also recommended intravenous bisphosphonate for patients with bone pain due to osteolytic lesions in multiple myeloma and breast cancer as adjunctive therapy. However, the current standards of care for cancer pain including analgesic and local radiotherapy should not be displaced by bisphosphonate 29,30.

A review of 30 randomised controlled studies including 3682 patients with bone metastasis from different primary tumors found that there was significant benefit in pain control with the use of bisphosphonates. The NNT was 11 at 4 weeks and 7 at 12 weeks. There are evidences to support the effectiveness of bisphosphonate in providing some pain relief for bone metastasis but insufficient evidence for immediate effect or as first line therapy. It has been suggested that bisphosphonates should only be considered when other analgesic and radiotherapy are inadequate for pain control 31.

Conclusion

The above discussion has only included the more recent studies on drug treatment of pain. However, in the context of cancer pain control, one should not forget other modalities of treatment, including non-pharmacological modalities and anaesthetic interventions. Besides, a comprehensive approach to cancer pain control should also include careful assessment and meticulous review. More evidence in each and all of these areas will contribute to better cancer pain control in the future.

References


Report on Scientific Activities

Dr Raymond LO
Scientific Committee

A scientific meeting jointly organised by Hong Kong Society of Palliative Medicine, Hong Kong College of Radiologists, and Hospital Authority COC in Clinical Oncology, was held on Nov 22nd 2006. The title of the lecture was Role of Research in Palliative Medicine, and our invited speaker was Prof P J Hoskins. Prof Hoskins is currently Consultant in Clinical Oncology & Professor in Oncology, Mount Vernon Hospital NHS Trust, Northwood, London, UK.

The lecture attracted an audience from both specialties of palliative care and oncology, together with other interested colleagues. In the lecture, Prof Hoskin emphasised and reminded us again the crucial importance of continuing research in the field of palliative medicine. He highlighted the lack of randomised controlled trials in his review of the published palliative care literature. He challenged the audience to review the basis and strength of evidence, for some of the current palliative treatment regimes. Prof Hoskins was deliberately provocative in his delivery, in order to alert us to the lecture theme of the important role of research. Although the lecture focused only on quantitative studies, it stimulated a useful exchange and sharing of ideas between our council members subsequently on both the quantitative and qualitative aspects of palliative care research.
Report on Scientific Activities

3rd Hong Kong Palliative Care Symposium,
16 September 2006, Hospital Authority Building

The Symposium was again a great success with an attendance of over 300 healthcare professionals, and everyone could attend the first choice workshop in the afternoon. Special thanks to all the members of the organizing committee, speakers, chairs, co-organizers, collaborators and our sponsor, Li Ka Shing Foundation. Encouraging comments received from many participants.

The speakers, Chairs, Co-organizers and collaborators
What’s coming up?

Our next Annual Scientific meeting is scheduled on Jan 11th 2007. We are delighted to have Prof Danai Papadatou to visit us again, and share further with us on Care for Patients who Die: Challenges for Health Care Providers in the Face of Death. She will also conduct two workshops for us in Hospital Authority on paediatric aspect of palliative care, and team issues in facing patient’s death. Please refer to the programme in the newsletter for further details and enrol early!
Hong Kong Society of Palliative Medicine

Annual Scientific Meeting

Co-organised with
COC in Palliative Care
Hospital Authority

Hong Kong Hospice
Nurses' Association

Jointly presents

Care for Patients who Die:
Challenges for Health Care Providers
in the Face of Death

Speaker: Prof. Danai Papadatou, Ph.D., Professor of Psychology,
Faculty of Nursing, University of Athens

Date: January 12, 2007

Time: 6:30pm to 8:00pm Lecture
8:00pm to 9:30pm Dinner

Venue: Lecture Theatre, M floor, Hospital Authority Building,
147B Argyle Street, Kowloon.

All are welcome!

Lecture and Dinner are free of charge.
Registration for lecture is not required.

For dinner registration, please fax to Ms. Rebecca Lee your name, institution,
contact phone number and email address (Fax No: (852) 2736 1926).
Please mark on the fax: "Seat Reservation for Dinner, ASM of Hong Kong Society of Palliative Medicine"

CME points for specialists and non-specialists / CNE points applied for.
AGM for Hong Kong Society of Palliative Medicine to be held at 6pm at the lecture theatre.

Co sponsored by:

JANSSEN-CILAG
a Johnson & Johnson company

Society for the Promotion of Hospice Care
Educational Meetings Calendar

**PMDM: Palliative Medicine Doctors Meeting**  (held every 2 months)
**MDM: Multi-disciplinary Meeting**  (held every 4 months)

Organisers: Hong Kong Society of Palliative Medicine
Training Subcommittee, COC in Palliative Care, Hospital Authority
Hong Kong Hospice Nurses' Association (for MDM)

Time: 5:30PM Refreshment
6:00PM – 7:30PM Lecture

Venue: Queen Elizabeth Hospital

Contact: Dr. Raymond Lo, Chairman, Scientific Subcommittee, HKSPM,
c/o Dept. of Medicine and Geriatrics, Shatin Hospital
Telephone: 26367500  Fax: 26477850

Or obtain the most updated information of the events at
http://www.medicine.org.hk

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<td>Our Lady of Maryknoll Hospital</td>
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<tr>
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<th>PMDM</th>
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<td>Queen Mary Hospital</td>
<td></td>
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</tbody>
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* Venue at the 12th Floor, R Block, QEH
**25 September 2007 is the Mid Autumn Festival

**Palliative Medicine Grand Round**  (monthly)

Tuesday at 6:00pm to 7:30pm

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<td>6 Feb 2007</td>
<td>Dr. HC Fan / Dr. KS Chan</td>
<td>Haven of Hope Hospital</td>
<td>Dr. WM Lam</td>
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<td>6 Mar 2007</td>
<td>Dr. Cindy Chan / Dr. Doris Tse</td>
<td>Caritas Medical Centre</td>
<td>Dr. KH Ng</td>
</tr>
</tbody>
</table>

Your suggestions and comments are most welcome. Please send to:
Dr. Doris Tse Man Wah, Chief Editor,
c/o Dept of Medicine & Geriatrics,
Caritas Medical Centre,
111, Wing Hong Street, Shamshuipo, Kowloon, Hong Kong.
Tel: 3408 7454  Fax: 2148 4399
E mail: hkspm@fmshk.com.hk

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Hong Kong Society of Palliative Medicine, the institution with which the author(s) is/are affiliated, unless this is clearly specified.
Membership Application/Renewal Form

1. PERSONAL PARTICULARS

Surname __________________ First name __________________________ (BLOCK LETTER)

Contact tel number __________________ (Office) __________________ (Mobile)

2. OTHER INFORMATION (Renewal members do not need to fill unless information has changed)

Corresponding Address (BLOCK LETTER) ____________________________

________________________________________ E mail________________________

Current Practice □ HA □ DH □ Private □ HKU □ CUHK □ Others

Name of institution __________________________________________________

Title (Dr. Mr. Ms. Mrs. etc) __________ Profession________________________

Membership Applied for / Renewed: □ Full Membership □ Associate Membership

I, the undersigned, is hereby applying for / renewing full membership / associate membership (delete if inappropriate) of Hong Kong Society of Palliative Medicine.

Applicant Signature: __________________________ Date: ________________

Proposer: __________________________ (BLOCK LETTER) Signature________

(for new application)

FOR OFFICIAL USE ONLY

Approved on _______________(date) for □ Full Membership □ Associate Membership

Membership fee paid for yr ___________ Cheque No__________ Amount________

Membership Information

Full Member – Any local registered doctors interested in the field; annual fee HK$150

Member – Other professional workers interested in the field; annual fee HK$50

Please send by mail the completed application form, together with a crossed cheque (payable to "Hong Kong Society of Palliative Medicine Limited") to:

Hong Kong Society of Palliative Medicine Ltd,

c/o Dr. Rebecca Yeung,

Dept of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital,

3 Lok Man Road, Chai Wan, Hong Kong.
Dyspnoea, anxiety, agitation, fear and restlessness are symptoms frequently encountered in patients with terminal cancer. The Palliative Care Team from the Haven of Hope Hospital found that midazolam, delivered by subcutaneous continuous infusion, has been very effective in controlling these very distressing symptoms.

The study was carried out over a period of 2 years from January 2004 to December 2005. During this period 541 in-patients passed away at the Palliative Care Unit at the Haven of Hope Hospital. Subcutaneous midazolam was used in 54 (10%) of these patients. The most common primary tumours were lung (41%), gastrointestinal (20%) and gynecologic (11%). The most common indications for using midazolam by subcutaneous infusion were dyspnoea (40%), agitation and restlessness (33%) and convulsions (22%), and fear and anxiety (13%).

The total midazolam dose over the first 24 hours (infusion and as needed) ranged from 2.5 mg to 17.5 mg, with a median dose of 5 mg. Eighty-two per cent of the patients required 7.5 mg or less. The maximal daily dose ranged from 2.5 to 45.0 mg, with the median dose of 7.5 mg. Seventy-six per cent of the patients used 10 mg or less per day. This was much less than the dosage used in most studies.

Midazolam administered by subcutaneous infusion was found to be effective in controlling dyspnoea in 19 out of 22 (86%), agitation and restlessness in 15 out of 18 (83%), fear and anxiety in 5 out of 7 (71%), and insomnia in 6 out of 7 (86%) of patients. Duration on midazolam infusion varied from less than 1 day to 20 days; with a median of 3 days.

The infusion was discontinued in six patients (11%); with one patient for each of the following reasons, including respiratory depression, drowsiness, family objection, uncontrolled convulsion, change to oral medication, and change to haloperidol because of concomitant nausea.

Use of Palliative Sedation in Advanced Lung Cancers in Caritas Medical Centre

MH Khemlani, OL Kwok, DMW Tse.
Palliative Care Unit, Caritas Medical Centre, Hong Kong.

Introduction:
Palliative sedation is used for refractory symptoms in palliative care including that for dyspnoea. This retrospective review aimed to study the use of palliative sedation in Caritas Medical Centre in patients with advanced lung cancer.

Methods:
This is an ongoing chart review of all advanced lung cancers admitted to the Dept of M&G of CMC from January 2005 to Jun 2005. Data on patient characteristics, indication and decision for palliative sedation, drugs used for sedation, and survival after commencement of sedation were retrieved.

Results:
A total of 110 patients were reviewed as at end of March 2006, of which 51 patients died in the palliative care unit, 33 patients died in acute wards. More than 20% of lung cancer patients dying in palliative care unit received palliative sedation mainly for refractory dyspnoea. All followed the existing guidelines on palliative sedation in CMC. All families were involved in discussion. More than 70% of patients themselves were involved in decision making. Survival post sedation ranged from 1 hour to 122 hours with a mean of 1.7 days.

Conclusion:
Palliative sedation has played a role in refractory dyspnoea in our palliative care unit, while none of the patients in the acute wards received palliative care sedation. The survival of patients after its commencement was comparable to that in international studies.
Free Paper Abstract

A Prospective Study to Identify Prognostic Factors of Survival in a Palliative Care Unit
PT Lam, MW Leung, CY Tse.
Palliative Care Unit, United Christian Hospital, Hong Kong.

Background:
Prognostic factors are important in survival estimates in end of life care. No formal studies on identification of prognostic factors have been performed in advanced cancer patients in local palliative care unit.

Objective:
To identify potential prognostic factors of survival in a local palliative care unit

Methods:
All advanced cancer patients who were admitted into the unit either as in-patient or out-patient between January and Decmeber 2002 were enrolled into this study. Potential prognostic factors including demographic data, tumour characteristic, blood parameters, functional status, co-morbidities, total symptom score and quality of life were recorded upon admission.

Results:
A total of 170 patients were eligible for analysis. Mean age was 69.3 yrs (SD 11.7) with 106 patients (62.4%) were male. The overall median survival was 76.5 days (IQR 30.8 - 160.3). The most frequent primary malignancy was lung (n=58, 34.1%), followed by liver (n=24, 14.1%) and lower GI tract (n=24,14.1%). By univariate analysis, eleven factors were found to affect survival, including age (p=0.04), no. of metastatic sites (p=0.001), peritoneal metastase (p=0.009), skin metastase (p=0.011), tachycardia (p=0.009), albumin (p<0.0001), white cell count (p=0.002), Karnofsky Performance Scale (KPS) (p<0.0001), Hamilton Depression Scale (KPS) (p=0.004), Edmonton Symptom Assessment Scale (ESAS) (p=0.003) and quality of life (p=0.002). Multivariate analysis revealed that only age (hazard ratio 0.84, 95% CI:0.73 - 0.96), no. of metastatic sites (hazard ratio 1.32, 95%CI: 1.13 - 1.56), albumin (hazard ratio 0.95, 95% CI: 0.92 - 0.98), KPS (hazard ratio 0.86, 95% CI: 0.78 - 0.96), ESAS (hazard ration: 1.21, 95% CI: 1.05 - 1.41) were independent prognosticators.

Conclusion:
Age, no.of metastatic sites, albumin, KPS and ESAS were independent prognosticators. Further study is needed to provide physicians with prognostic instrument applicable in local clinical settings.

Case presentation: A gentleman with multiple pathological fractures
Dr. Jasmine Chan, Palliative Care Unit, United Christian Hospital.
chantm4@uch.ha.org.hk

Background
Mr. C Chung was an 84-year-old gentleman who lived with wife in a public housing estate. He enjoyed independent activities of daily living. He had past history of gastritis, bilateral tinnitus, cataract and anxiety neurosis. Mr. Chung presented with liver abscess in 2/2004 and was incidentally found to have radiological left renal cell carcinoma (RCC) by CT abdomen. He refused nephrectomy and so was put under conservative management.

History of present illness
He first presented to the orthopaedic team with pathological fracture of right proximal humerus after a minor injury in May 2005. Bone biopsy revealed metastatic renal cell carcinoma and palliative radiotherapy was given in November 2005. For some unknown reasons, bone scan was not done.

In May 2006, Mr. Chung sustained another unprovoked pathological fracture of right femur. Long proximal femoral nailing was done and bone biopsy confirmed metastatic renal cell carcinoma again. Mr. Chung had to walk with quadripod during the period. He was transferred to a convalescent hospital for rehabilitation subsequently.

While staying in the convalescent hospital, Mr. Chung experienced another pathological fracture over the left humeral shaft upon transferral from bed.
to chair. He was transferred back to the acute hospital. Palliative radiotherapy was given to right femur and left humerus. However, after transferral back to acute hospital, the last fracture happened while turning in bed, affecting the trochanter of left femur. Conservative management was decided after repeated conjoint interview among the palliative care team, orthopaedic team, patient and family.

Mr. Chung became bedridden and was totally dependent due to multiple long bone fractures.

In summary, this was an 84-year-old gentleman with multiple pathological fractures over bilateral humerus and femurs secondary to bone metastases of renal cell carcinoma. Internal fixation was done for the fractured right femur and palliative radiotherapy was given to right and left humerus and right femur. The fractured left hip was managed conservatively. He became bedridden as a result of multiple fractures.

**Discussion**

Metastatic bone disease is the most common cause of destructive lesion of the skeleton. There is high fracture rate in metastases from lung cancer, but relatively unusual in prostate cancer, where bone metastases are predominantly sclerotic. The most common site affected is proximal femur. Among these fractures, femoral neck, sub-trochanteric and inter-trochanteric region comprise 50%, 20% and 30% respectively. In addition, pathological fractures require extended time to heal and 50% would never heal at all. 1

The investigations include baseline laboratory tests and imaging. The diagnosis should be confirmed in patients with a history of cancer and an isolated metastasis, 2 for example, by needle biopsy. For surgical planning, X-ray of entire femur for fracture neck of femur is indicated as all lesions must be by-passed. For acetalubar side of the joint, computed tomography or magnetic resonance imaging of the pelvis is considered. 1

Lesions with high risk of fracture require surgical stabilization using prophylactic osteosynthesis. Painful, low-risk lesions can be treated conservatively using external beam radiotherapy, chemotherapy, hormonal therapy or regular infusion with bisphosphonates. 3

Mirels’ scoring system was suggested to be used to predict the risk for impending fractures. The scoring depends on four variables, namely location over the extremity, size of the fracture, pattern of bone destruction and pain. Others suggested that there was no definite risk factor to adequately predict the occurrence of a pathological fracture of a femoral metastasis. 3 Most importantly, the quality of life of a patient with a limited life expectancy is the prime concern.

Surgical management of pathological fractures of the proximal femur includes intramedullary nails, plate fixation and prosthetic devices. Post-operative external beam radiotherapy was found to decrease the rates of secondary procedures and improved functional status of the patients. In the retrospective study by Townsend et al, 15% of patients treated with surgery alone required a second orthopaedic procedure due to increasing pain and/ or implant loosening. In patients treated with postoperative irradiation, only 3% required a secondary procedure.

Post-operative external beam radiotherapy is commenced within 2 to 4 weeks of surgery, typically after the wound has adequately healed. Patients with renal cell carcinoma often receive high doses. Improvement in the severity of pain may occur within as soon as 48 to 72 hours of initiation of therapy. 4 Many trials have attempted to identify the fractionation regimen that results in the best pain control for bone metastases with a low risk of side effects. No regimen has been shown to be consistently superior. 4

Another option is bisphosphonate. In three separate studies involving 1,518 enrolled patients, Pamidronate has demonstrated significant clinical benefit in patients with osteolytic bone lesions from breast cancer and multiple myeloma. Zoledronic acid demonstrated efficacy comparable with that of Pamidronate. 5 Newer bisphosphonate, such as Ibandronate, also demonstrates efficacy in treating metastatic bone disease from breast cancer. More clinical trials are currently ongoing to assess its effect in other tumour types. 6

**Reference**

Use of Antimicrobials in Terminally ill Cancer Patients: Experience of a Clinical Oncology Unit

Dr. KH Wong, Dr. KK Chau
Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong
Correspondence: wongkh@ha.org.hk

Introduction

Cancer patients are particularly susceptible to infections due to a variety of disease-related and therapy-induced factors. Various retrospective studies reported variable incidence of infection in advanced cancer patients, probably related to their different clinical settings and different definition of infection. Although infection is one of the leading causes of death in cancer patients, there is little information describing the management of infections in terminal cancer patients when dying is eminent. Under such clinical circumstances, it is difficult to make the decision on whether to treat or not to treat, and how to treat the infection.

A survey was conducted to study the pattern of the use of antimicrobials in terminal cancer patients in their last two weeks of life, in the acute hospital setting and in the extended bed setting of a clinical oncology unit.

Methodology

The clinical records of the consecutive cancer patients who died in the acute beds of the Department of Clinical Oncology, Queen Elizabeth Hospital from 1st January to 28th February 2006, and the clinical records of the consecutive cancer patients who died in the extended beds of the same oncology unit at the Hong Kong Buddhist Hospital from 1st January to 31st May 2006 were retrospectively reviewed.

In this study, the cancer patients who died of cancer were arbitrarily divided into two groups: the group of patients under “active treatment” if the patients had received chemotherapy or radical curative treatments within one month before death; and the group of patient under “symptomatic treatment” if the patients had not received chemotherapy or radical curative treatment within one month before death. The pattern of the use of antimicrobials for the patients who were under “symptom treatment” in their last two weeks of life during their last admission was studied. The demographic data of the patients, the indications and the outcomes of the use of the antimicrobials were recorded.

Results

During the study period, 81 cancer patients died in the acute beds of the department and 100 cancer patients died in the extended beds of the same department. Seventy-seven acute bed patients and ninety-three extended bed patients had the clinical records available for review.

Out of the 62 acute bed patients who were under “symptomatic treatment”, 50 received 59 courses of antimicrobials in their last two weeks of life. However, only 30 out of the 91 extended bed patients under “symptomatic treatment” received 35 courses of antimicrobials in their last two weeks of life. The patient characteristics are summarized in table 1.

Infection Pattern Leading to Use of Antimicrobials

The clinical diagnosis and the symptoms leading to use of the antimicrobials and the final diagnosis of infection are listed in table 2.
In both acute hospital and extended care settings, chest infection and urinary tract infection were the main clinical diagnoses leading to the use of antimicrobials. For 24 episodes of infection (40%) in the acute beds and 10 episodes of infection (28%) in the extended beds, the definite source of infection could not be identified. Thirty-seven % infection in the acute beds and 40% infection in the extended beds were confirmed by culture. The organisms identified in the acute bed patients included

- Candida (7 cultures),
- Pseudomonas (3 cultures),
- Klebsiella (3 cultures),
- E. coli (3 cultures),
- Staph. Aureus (3 cultures),
- MRSA (3 cultures),
- Enterococcus (2 cultures),
- Morazella catarrhalis (1 culture),
- Gram –ve bacilli (1 culture) and
- Streptococcus (1 culture),

and the microorganisms identified in the extended bed patients included

- Pseudomonas (6 cultures),
- Klebsiella (4 cultures),
- E. coli (2 cultures),
- Staph. Aureus (1 culture) and
- Acinetobacter (1 culture).

### Table 2: Clinical diagnosis and symptoms leading to the use of antimicrobials, and the final diagnosis of infection

<table>
<thead>
<tr>
<th>Clinical Settings</th>
<th>Acute Beds</th>
<th>Extended Beds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Course of antibiotics</td>
<td>59</td>
<td>35</td>
</tr>
<tr>
<td>Clinical diagnosis leading to use of antimicrobials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest infection</td>
<td>26 (44%)</td>
<td>20 (57%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9 (15%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Occult sepsis leading to deterioration of general condition</td>
<td>10 (17%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Wound / soft tissue infection</td>
<td>4 (7%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (18%)</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Symptoms leading to use of antimicrobials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough / symptom / shortness of breath</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>Fever</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Deterioration of general condition</td>
<td>25*</td>
<td>8</td>
</tr>
<tr>
<td>Dysuria / frequency of urination</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Oral flush</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>No specific symptom</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Final Diagnosis of infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite source of infection could not be identified</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Chest infection</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

* 7 patients had deterioration of general condition as the sole symptom

### Pattern of the Use of Antimicrobials

The pattern of the use of antimicrobials is summarized in the table 3. For the acute bed patients, out of the 59 courses of antimicrobials given in the last two weeks of life, one course commenced before transferal from other unit, 31 in the last second weeks, 13 in the period between the last 48 hours and the last one week, and 14 in the last 48 hours (24%). For the extended bed patients, out of the 35 courses of antimicrobials given in the last two weeks of life, 4 courses commenced before the last two weeks, 4 commenced at the acute beds before transferal to the extended beds, 4 in the last second week, 11 in the period between the last one week and the last 48 hours, and 10 in the last 48 hours.

Comparing the use of antimicrobials in both acute bed and extended bed settings, a higher proportion of acute bed patients received intravenous antimicrobials and combination antimicrobials regimens. Seventy-two percent of the courses of antimicrobials received by the acute bed patients had at least one antimicrobial administrated by intravenous route while only 6% courses of antibiotics received by the extended bed patients had at least one antimicrobial given by intravenous route. Eleven episodes of
of the acute bed patients (17%) had received combination antimicrobials regimen while only two episodes of infection of the extended bed patients (6%) had received combination antimicrobials regimen. The most commonly used antimicrobials in the acute beds were augmentin, ciprofloxacin and cefuroxime and the most commonly used antimicrobials in the extended beds were augmentin and ciprofloxacin. “Big Gun” antibiotic (8 Tazosin, 4 Sulpherazone, 1 Ceftazidime) had been used in some acute bed patients but not in the extended bed patients.

**Outcome**

With the use of antimicrobials, 22% of the suspicious infections in the acute bed patients improved and also 30% had symptoms improved, while 28.5% of the suspicious infections in the extended bed patients improved and also 34% had symptoms improved. The outcome and the frequency of the symptoms improved are summarized in table 4.

### Table 3: Pattern of the use of antimicrobials

<table>
<thead>
<tr>
<th>Clinical Settings</th>
<th>Acute Beds</th>
<th>Extended Beds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients under symptomatic treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On antimicrobials in the last two weeks of life</td>
<td>80%</td>
<td>36%</td>
</tr>
<tr>
<td>On antimicrobials in the last 48 hours of life</td>
<td>79%</td>
<td>30%</td>
</tr>
<tr>
<td>Proportion of antimicrobials courses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commenced within the last 48 hours of life</td>
<td>24%</td>
<td>28%</td>
</tr>
<tr>
<td>Having intravenous antimicrobials as one of components</td>
<td>72%</td>
<td>6%</td>
</tr>
<tr>
<td>Combination regimen</td>
<td>17%</td>
<td>6%</td>
</tr>
</tbody>
</table>

### Discussion

It is difficult to make the decision whether to use the antimicrobials in treating infection of terminal cancer patients when dying is eminent. Under such clinical circumstances, various studies do not demonstrate survival benefits of the use of antimicrobials\(^3\,^5\) and antimicrobials could cause discomfort to the patients such as adverse drug effects, more diagnostic tests and occasionally an intravenous line if intravenous antimicrobials are given. However, the use of antimicrobials under such clinical circumstances, as shown in our series and other series\(^6\,^7\), could improve the infection in some patients and hence provide a certain degree of symptom control. Performance status and estimated life expectancy of the patients, type, severity and symptomatology of the infection, and expectation of the patients and patients’ family together with the clinical training and experiences of the attending physicians are all inter-related to determine the use of antimicrobials in the terminal cancer patients in different clinical settings.

This series shows a higher frequent use of antimicrobials in terminally ill cancer patients cared in an acute hospital setting than in an extended care setting (80% versus 36% in last two weeks of life); and a more aggressive use of antimicrobials in the acute hospital setting, using more intravenous antimicrobials and more combination antimicrobial regimens. As shown in table 5, various series have demonstrated different incidence rates of infection at different clinical settings\(^1\,^6\,^8\,^9\). This might partially account for the difference in the proportion of patients on antibiotics in different clinical settings.

### Table 4: Outcome of use of antimicrobials

<table>
<thead>
<tr>
<th>Clinical Settings</th>
<th>Acute Beds</th>
<th>Extended Beds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection subsided</td>
<td>22%</td>
<td>28.5%</td>
</tr>
<tr>
<td>Overall symptom improved</td>
<td>30%</td>
<td>34%</td>
</tr>
<tr>
<td>Symptoms improved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deterioration of general condition</td>
<td>2 (48%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Cough / sputum/ SOB</td>
<td>10 (34%)</td>
<td>8 (47%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>4 (66%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>Fever</td>
<td>6 (35%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>1 (100%)</td>
<td>-</td>
</tr>
<tr>
<td>Oral flush</td>
<td>1 (100%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Purulent discharge</td>
<td>-</td>
<td>1 (100%)</td>
</tr>
</tbody>
</table>
In the acute hospital setting, most advanced cancer patients under “symptomatic care” are admitted through casualty or clinic with fair general condition. On the other hand, their counterparts cared in the extended beds would be in more stable condition upon transference from the acute wards. The patients and relatives would have different expectations in these two clinical settings. Our series shows that patients would stay longer in the extended wards before death than in acute wards (median length of hospital stay: 20 days in extended beds versus 12 days in acute beds). A longer hospital stay could provide adequate time for the attending doctor to develop a rapport with the patient. They would have better communication with the patients and their relatives about the issues of end of life care. This could help the attending doctors, the patients and the patients’ families to reach a consensus on the use of antimicrobials in end of life care. Most of the attending oncologists taking care the cancer patients in the extended beds in our series are specialists in clinical oncology with much clinical experience and training in palliative medicine. Such clinical training could further help the attending doctors to make appropriate decisions in end of life care of the patients and to avoid futile treatment for the patients.

Conclusion

This study shows that a significant proportion of terminal cancer patients had received antimicrobials for treatment of infection in their last two weeks of life, and the use of antimicrobials was more frequent in the acute hospital setting than in the extended care setting of a clinical oncology unit. About 25% patients had infection improve and 30% patients had symptoms improve after the use of antimicrobials. For the terminal cancer patients when dying is eminent, the main aim of the use of antimicrobials should be symptom control. Before making the decision on the use of antimicrobials under such clinical circumstances, we should balance the possible risks and benefits of the use of antimicrobials with respect to the expectation of patients and their family. Adequate communication and competence in end of life care could facilitate the decision making in this aspect.

Reference


| Table 5: Incidence of infection in advanced cancer patients at different clinical settings |
|---------------------------------|-------|-----------------|-----------------|
| Series                        | Number of patients | Clinical Settings              | Incidence of infection |
| Ahronheim et al              | 84    | Teaching Hospital | 83%                     |
| Bauduer et al                 | 81    | Oncohaematology Unit | 40%               |
| Pereira et al                 | 100   | Acute Palliative Care unit | 55%               |
| Vitetta et al                 | 102   | Hospice unit       | 36.3%               |
COURSE ANNOUNCEMENT

END-OF-LIFE CARE TRAINING FOR LAY CAREGIVERS - FAMILY CAREGIVERS, HIRED CAREGIVERS, AND VOLUNTEERS
A new program to meet the needs of the lay caregivers in caring for people living with a life limiting illness

Date: Jan 20 & 27, Feb 3 & 10
Time: Saturdays 2-5pm
Venue: SPHC in Central
Trainer: Faye Chan, RN, Program Development Director
Content: palliative approach to end of life care, symptom management & psychosocial support, communication skills, anticipatory grief
Format: small group, interactive learning

Postgraduate Diploma and MSc in Palliative Medicine (With paediatric option)
A quotable postgraduate qualification by distance learning

Wherever you are in the world, you can now gain qualifications from Cardiff University - a centre of academic and clinical excellence. The next programme begins in September 2007 and consists of three Phases to Masters-level, or two Phases to Diploma-level. These have been specifically designed to meet the varying needs of busy medical practitioners working in differing clinical settings across the globe. They are:

* modular (6 modules per phase)
* directed to distance-learning
* Internet-based
* culturally sensitive
* based on reflective learning

While most of the programme is distance learning, there are two residential blocks during the programme which focus on communications skills and enable students to discuss topical issues in depth. The programme also incorporates video-based communications skills assessment and a final written examination for Phase II.

Phases I & II are clinically orientated, with Phase II being particularly suitable for higher specialist trainees in palliative medicine, leading to the award of the postgraduate Diploma. Phase II offers students the opportunity to focus on paediatric palliative care issues.

Phase III focuses on original research, leading to the MSc degree. Each phase is based on the internationally renowned palliative medicine courses that have been delivered from Cardiff since 1989.

Phases II & III are quotable qualifications in Hong Kong, accredited by the Hong Kong Medical Council.

The demand for places is expected to be high, so an early application for September 2007 entry is strongly recommended.

Please visit our website to obtain further information and an application pack.

www.pallium.cardiff.ac.uk
Hike for Hospice 2007 is to be held on Sunday, 4 February 2007. This year, we will be taking you to one of the Hong Kong's most picturesque areas - Hok Tau, Fanling.

There are two categories of participation: Team Category (4 to 6 hikers) and Individual Category. All donations will go into supporting our "end-of-life care" training for carers and bereavement support at the Jessie and Thomas Tam Centre. For details, please go to our website: www.hospicecare.org.hk/eng/hike2007 or call us at 2868 1211.

World Hospice Palliative Care Day - Latter Life Forum on October 7

Co-organized with HA Health InfoWorld, the Forum entitled “What is a Good Death to Me?” was held as part of the outreaching activities for the World Day. We were honored to have a group of renowned speakers to address a wide spectrum on the topic. Invited speakers included Mr. William Tan, Mr. Alain Yip, Master Sik Hin Hung, Prof. Tao Kwok Cheung, Dr. Yvonne Mak and Ms. Connie Chow, and Mrs Yvonne Siu, the convener.

The Forum was greeted with enthusiasm.

“I disagree...” - Participants were very involved.