HOT SPOT

SUNNYBROOK & WOMEN'S
Sunnybrook and Women's College Health Sciences Centre

Guest editor's note

By Toni Barnes, MD, FRCP

Welcome to the first issue of **Hot Spot** for 2005. In this issue, Dr. Szumacher summarizes the findings from her study looking at patients' treatment preferences with radiotherapy for bone metastases. This is very important clinically as the majority of patients seen in the RRRP receive radiotherapy for painful bone metastases. We are pleased to have Dr. Librach write the insert on the use of methadone for cancer pain. Ms. Karen Faith has written an article on the difficulties surrounding hospital CPR policy. Dr. Vachon discusses the difficulties of parenting teens during a cancer experience. Dr. Hayter provides us with an interesting historical vignette. In the research column, Dr. Wong looks at "Radiotherapy-induced emesis (RIE) – should dexamethasone be added to 5HT3 antagonist as prophylaxis?".

We hope that these contributions provide interesting and informative reading.

Treatment of bone metastases with palliative radiotherapy: Patients' treatment preferences

By Ewa Szumacher, MD, FRCPC

Radiotherapy is an effective method of providing pain relief for symptomatic bone metastases. Radiation oncologists in Canada, when treating patients with bone metastases, use two fractionation regimens: 2000cGy in five fractions, or 800cGy in one fraction. Given that outcomes are similar in palliative radiotherapy studies investigating longer versus shorter radiotherapy fractionation regimens, we were interested in asking our patients, if they had a choice, what treatment regimen they would prefer and why. The primary endpoint of the study was to determine the proportion of patients who would like to participate in decisional preferences for palliative radiotherapy for bone pain due to bone metastases. The secondary endpoint was to determine patients' preferences for the palliative radiotherapy regimen (2000cGy in five fractions versus 800cGy in single fraction), and to define factors influencing patients' decisions.

Patients with painful bone metastases who required palliative radiotherapy at the Toronto Sunnybrook Regional Cancer Centre were eligible for the study. To determine patients' decisional preferences, we used a questionnaire that described three potential roles that patients may play in the decision-making process: active, collaborative and passive. Patients who chose either an active or collaborative role subsequently participated in the second part of the study in which we investigated patients' preferences for one of two palliative radiotherapy regimens (2000cGy in five fractions versus 800cGy in single fraction).

To help patients with the decision regarding palliative radiotherapy regimens, we developed a decision board instrument as a visual aid. The information on the decision board was derived from multiple studies investigating the role of palliative radiotherapy for bone metastases. The decision board, using the trade-off technique, presented the differences and similarities of the two palliative

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Parenting teens during a cancer experience

By Mary L.S. Vachon, RN, PhD

As a clinician, I have often said that if you have teenagers, you should not get cancer. It is enough to deal with one family developmental crisis at a time. However, cancer doesn't wait to be invited at a convenient time and often arrives while there are many other family issues of concern.

In 2002-2003, a Parenting Your Teens Through Your Cancer Experience Group was started at Wellspring. The group stopped with the SARS epidemic and has recently resumed. Parents are offered the opportunity to meet with others in a similar situation to discuss which of the crises they are going through are related to their cancer experience and which are common to parents of teens.

Issues of concern include: information exchange, the hereditary nature of some cancers, being a single parent, dealing with multiple cancers or other illnesses in the family and dealing with death and dying. It is often difficult to know how much information to share with teens. If parents try to give more information than the teen wants to know at a particular point in time, the parent is likely to meet with resistance or being told that the teen already knows the information. The same teen may then be busy finding information on the internet, which may or may not be accurate. Teens will often resist being given information about a parent's disease or being told that the parent's disease is progressing because of deep fears about what will happen to them and the world as they know it. Adolescence is a time when one's peer group is of maximum importance. Teens will often want to spend time with their peers, ignoring parents and their needs. As long as the teen is with peers, he or she can pretend that life is normal. Parents who want their teens to spend time with them are often hurt and disappointed when the teen wants to be out, and when the teen is angry because the parent cannot maintain normal activities such as car pooling or being available to pick them up late at night because of exhaustion due to treatment. It is helpful for parents to be able to share their frustrations and hurt feelings with others in the same situation and learn that their child is not unique. Parents are able to share helpful suggestions regarding how to work in difficult conversations – in the car, at bedtime, going out for lunch, or calling a family meeting sometimes works.

When there have been other cases of cancer in the family, the teen may assume that if the other person died, then their parent will as well, or if the other person has lived, then the parent will and there is no big deal to be made about it. Teens may then feel that it is a particularly cruel twist of fate if their parent is to die when others have lived. They may also fear developing the illness and take the attitude, "my life may be short, so just enjoy it and don't plan for the future, as I may develop cancer at a young age."

When there are other cancers or family illnesses, both parents and teens can find themselves feeling overwhelmed. If the teen has a chronic illness and has always counted on the parent to be available to care for him or her, it might be challenging to assume more responsibility for oneself during the parent's treatment. Some teens will rise to this challenge, while others may consciously or unconsciously display more of their needs in order to show the parent, "hey, I'm the kid with the needs, you have no right to have your own needs and think that they should supplant mine."

Being a single parent to a teen can be challenging at best, particularly if there are difficulties in the relationship with the other parent, or if the other parent is not available either through illness or death. When one parent has died and the other is diagnosed with cancer, the teen may feel very threatened and respond with acting out behaviour which, in some ways, is meant to unconsciously signal to the parent with cancer, "you better not die and abandon me as I can't take care of myself."

Dealing with issues of "what if I am to die," are challenging to all parents, particularly if there are issues with non-custodial parents. Being able to share these concerns can help to make the burden easier.

Call Wellspring, Odette House at (416) 961-1928 to learn more about the program, or contact me at maryvachon@sympatico.ca.

Mary Vachon, RN, PhD, is a psychotherapist in private practice.

Treatment of bone metastases with palliative radiotherapy: Patients' treatment preferences

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radiotherapy regimens. After the patients chose the radiotherapy treatment, they completed a questionnaire about the factors that influenced their choices.

From January 2000 to August 2003, 101 patients were eligible and entered the study. Our results indicated that 77 patients (76%) wanted to play an active or collaborative role. The majority of our patients favoured one single fraction of palliative radiotherapy, 55 of 72 patients (76%) and only 17 of 72 patients (24%) preferred five-day treatment.

The multivariable analysis of the factors influencing patients' decisional choice indicated that patients were more likely to select 800cGy in one fraction because of the convenience of the treatment plan, and more likely to prefer 2000cGy in five fractions because of decreased likelihood of bone fracture. This was consistent with the nonparametric analysis which identified these two factors along with overall quality of life as being different between patients choosing the two treatment options.

There is controversy about how much patients should participate in the decision-making process about their treatment. Some authors argue that patients should always be offered a choice; others feel that physicians, because of their experience and medical knowledge, might be in a better position to judge and decide on the optimal treatment.

In conclusion, this study showed that the majority (76%) of our patients with incurable cancer, after understanding treatment risks and benefits, will be able to make their own treatment decisions.

Hospital CPR policy: Solution, prevention or band-aid?

By Karen Faith, MEd, MSc, RSW

Mr. J was a 45-year-old cancer patient with metastatic spread who, after the second round of chemotherapy, developed pneumonia requiring respiratory support. While in critical care, the patient's spouse was told that if Mr. J arrested, he would not receive cardiopulmonary resuscitation (CPR), however, everything to ensure his comfort would be done. The team's approach was in accordance with the hospital's CPR policy. The patient's spouse, shaken by such news, asked for patient relations to investigate why the critical care team was "giving up" on her husband.

Policies regarding CPR are roughly 25 years old. These policies provide a framework within which health care professionals can establish a plan of care for seriously ill patients in the event of a cardiac arrest. Consideration is given to the medical indications, standards for care, the values and wishes of the patient. Guidelines for informing patients, family members and substitute decision-makers of the patient's care plan of no-CPR are included. Principle objectives of these policies are to avoid treatments considered futile or harmful, to reduce the potential for conflict or confusion in the event of a cardiac arrest and to ensure that the patient's preferences are respected. However, policies alone do not always ameliorate conflict or confusion in end-of-life decision-making. A comprehensive approach emphasizing advance care planning, effective communication, collaboration and multidisciplinary team functioning is also needed.

There is evidence that only a minority of patients with chronic or serious illnesses discuss their preferences about CPR with their physicians. Patients and their families may hold unrealistic expectations or misinformation regarding the outcome or effectiveness of CPR. A lack of comprehensive training for physicians on addressing end-of-life preferences with chronically or seriously ill patients may be part of the problem. Although there is significant support for a deliberative approach based on providing relevant information and effective communication, the approach used by health care teams is variable and frequently constrained by a lack of time, coordination and problematic multidisciplinary team functioning.

Policies on CPR are best situated within a comprehensive quality of end-of-life care approach. Such an approach would support advance care planning with patients and their families. In addition, health care teams would require training, resources, time and opportunity to support effective communication strategies for decision-making. Lily et al. (2003) support using communication interventions in intensive care situations like the case involving Mr. J. This strategy requires that meetings be held within a set period of time after ICU admission with patients and/or substitute decision-makers. Goals for care, medical indications, patient values and preferences are discussed while establishing a period of trial for the current course of treatment. Treatment plans are then revisited at a set time. Within such a framework, all treatment options including CPR can be discussed using a comprehensive, multidisciplinary and collaborative approach. Policies or guidelines regarding CPR require that health care teams meet their ethical obligations by upholding standards for care, striving to reach consensus when there is disagreement, while modelling respect and compassion.

Karen Faith is a clinical ethicist at Sunnybrook and Women's College Health Sciences Centre.

Historical Vignette:

Alfred Hardisty Sellers: Ontario's pioneer in cancer statistics

By Charles Hayter, MA, MD, FRCPC

One of the most important steps in public health in Ontario took place in September 1936, when Dr. Alfred Hardisty Sellers (1907-1988) was appointed the first medical statistician to the Department of Health. Sellers was a Toronto native who received both his MD and a diploma in public health from the University of Toronto.

One of Sellers' mandates was "to adequately assay the value of the program for cancer treatment so heavily subsidized by the government" and, almost immediately, he set up a centralized system of recording and reporting for the then seven cancer clinics in Ontario. Data on cancer incidence, mortality and treatment were collected and analyzed by Sellers and formed the basis of a series of "Statistical Reports on Cancer," the first of which appeared in 1937. These reports were (and remain) invaluable sources of information about the numbers of new cases seen in each clinic, the types of cancer treated, and methods of treatment employed.

It is interesting that Sellers' reports identified weaknesses of the cancer program that have persisted to today. First, he found geographic inequalities in access to the cancer clinics. The ratio of cases treated in a cancer clinic to population was highest in the counties where the cancer clinics were located and lowest in more remote counties. This data gave support to critics of the cancer program who had argued that over-centralization was not appropriate for a large province with a scattered population such as Ontario.

Sellers' second important observation was the low proportion of cancer cases being seen in the clinics. In 1938, for example, he found that only 30% of the estimated 1,400 cases of breast cancer in the province were being seen in a cancer clinic. Clearly, a large number of cancer cases were still being assessed and treated outside the formal cancer system, a phenomenon largely explained by the continuation of cancer treatment in private clinics and hospitals around the province. Sellers also uncovered surprising variations in treatment practice across the province. He found for example, that the use of radium alone to treat the same condition varied markedly. For example, the use of radium alone to treat skin cancer varied from 5% of cases in Hamilton to 88% of cases in Ottawa. Similar discrepancies were noted for oral and uterine cancer.

Sellers was also active in international cancer statistics, and played a leading role in the development of the TNM (Tumour-Node-Metastasis) staging classification for cancer.

Research Corner

Radiotherapy-induced emesis (RIE) – Should dexamethasone be added to 5HT3 antagonist as prophylaxis?

By Rebecca Wong, MB, ChB, MSc, FRCP, Associate Professor, Radiation Oncologist, Princess Margaret Hospital

Nausea and vomiting secondary to radiotherapy treatments can result in significant impact on the quality of life and, potentially, compliance to treatment. The risk for nausea and vomiting is site, field size and dose dependent. For example, a fractionated course of radiotherapy to the stomach region is associated with RIE in about 50% of cases, a single fraction of hemibody irradiation in 80%, while treatment to the pelvis alone is low in emetogenic potential with risks in the order of 10%. Patient factors such as tendency to motion sickness, prior use of chemotherapy or alcohol could further modify this. The mechanism behind RIE is multiple. For nausea and vomiting related to abdominal irradiation, serotonin released from the enterochromaffin cells of the gastrointestinal tract likely plays a major role in RIE, through interactions with visceral afferent fibres and the 5HT receptors. Brain radiotherapy on the other hand, typically causes nausea and vomiting through precipitating raised intracranial pressure from edema associated with the underlying neoplastic process, or direct stimulation of the central nuclei.

Typical patients who may be at risk of radiation-induced nausea and vomiting include those with gastrointestinal malignancies, lymphoma, seminoma, gynaecological malignancies and patients receiving palliative radiotherapy to the thoracolumbar spine, or hemibody irradiation for bone metastases, often for pain relief. Nausea and vomiting can commence as quickly as half an hour after the radiotherapy. Prophylactic treatments for high risk patients represent the best strategy for the management of these patients.

Several treatment guidelines have been published on the use of antiemetics in radiation-induced emesis with consistent recommendations. For patients receiving moderate or highly emetogenic radiotherapy, prophylactic therapy was recommended. The use of 5HT3 antagonists was uniformly supported, while a dopamine receptor antagonist was also advocated. What the current evidence is lacking, however, is how 5HT3 antagonists should be best used.

The NCIC CTG with an established track record in conducting trials in chemotherapy-induced emesis, published the results of its first study on radiation-induced emesis (SC12) in 1999. In this study, dexamethasone was found to be effective in the prophylaxis of RIE, providing complete control of emesis in over 70% of patients compared with 49% in the placebo group. It was observed that the majority of emetic episodes occurred within the first few days of radiotherapy. This led to a hypothesis around whether the use of a brisk, more aggressive schedule of antiemetic, such as combination ondansetron and dexamethasone (OndDex), can result in superior and durable control of emesis for the remainder of the radiotherapy. SC19 was designed to address this hypothesis.

NCIC CTG SC19

Through the collaborative effort of 15 radiotherapy centres across Canada, SC19 was successfully completed, and the results were presented for the first time at the 2004 annual meeting of the European Society of Radiation Oncology in Amsterdam. Two hundred and eleven patients were randomized between ondansetron (8mg bid) and dexamethasone (4mg od). Treatment arms were well balanced.

When focusing on the first five days of radiotherapy, while the study found no significant difference in complete control of nausea or vomiting between the two treatment arms (absolute control rate of OndDex 78% and OndPlac 71% p = 0.14), there was a trend towards better control of nausea with OndDex (50% vs. 38%, p=0.06).

It is perhaps more thought-provoking when the effect of OndDex x5 fractions on the subsequent emetic profile was examined. Emesis control was found to be significantly better for the OndDex group as was hypothesized. However, the absolute proportions were suboptimal for this strategy to be useful alone. (OndDex 23% vs. OndPlac 12%, p = 0.02). Nausea was better controlled although this is not statistically significant (15% vs. 9%, p = 0.14).

SC19 also lent itself to examine the effect of combined OndDex x 5 fractions followed by ondansetron rescue, as compared to the same without OndDex upfront. Patients enrolled in this study were prescribed rescue packs, prochloperazine 10mg tid prn between fraction 1-5, and ondansetron 8mg bid after fraction 5. Examination of the nausea profile, rescue medication use, and quality of life profiles across the entire treatment period therefore provides evidence to address the effectiveness of the overall strategy.

The average nausea score for OndDex (plus rescue) was superior (1.28 vs. 1.39, p = 0.03) and the proportion of patients who took rescue antiemetics was lower in the OndDex (plus rescue) arm (70% vs. 79% p = 0.09). The cumulative amount of rescue ondansetron taken was similar between the arms 7 +/-4.6 number of tablets. Patients on the OndDex arm had better QoL in appetite both at fraction 5 and by fraction15.

SC19 represents a dedicated effort from the Canadian radiation oncology community to address the best way of reducing the impact of radiation-induced emesis. The effort identified that **prophylactic combined OndDex x 5 fractions** was superior to ondansetron alone in improving nausea, even after prophylaxis has been discontinued. However, this strategy alone is suboptimal. SC19 provided evidence that the use of **prophylactic combined OndDex x 5 fractions, followed by ondansetron taken prn,** provides superior nausea control for the entire treatment period and likely represents the best strategy to prevent nausea and vomiting at this time.

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HOT SPOT

By S. Lawrence Librach MD,CCFP,FCFP, W. Gifford Jones Professor Pain Control & Palliative Care University of Toronto, Director, Cancer Pain Clinic, Toronto Sunnybrook Regional Cancer Centre, Toronto, Ontario

Methadone for cancer pain: An analgesic with a difference

Background

Methadone is a synthetic opioid first synthesized as an analgesic in Germany in the Second World War as an alternative to morphine, which was in short supply. For years in North America, it has been used as a drug for maintenance and withdrawal therapy for opioid addicts. In recent years, there has been a resurgence of interest in its use as an analgesic. Methadone has somewhat unique pharmacodynamic and pharmacokinetic properties that make it a preferred drug in some pains. It also has the advantage of being relatively inexpensive compared to other opioid formulations.

Key aspects of the pharmacology of methadone

- Consists of a racemic mixture of D and L isomers.
- The L-isomer is considerably more potent for analgesia.
- The D-isomer is less of an analgesic, but it does have properties that make it antitussive. This isomer also has an antagonistic effect on the NMDA receptor that has a role to play in neuropathic pain.
- Methadone acts at both mu and delta opiate receptors to produce analgesia.
- Methadone is completely absorbed through the gastrointestinal mucosa, but some partial metabolism occurs within the gut wall making bioavailability about 80%, considerably better than morphine or hydromorphone.
- More highly protein bound than morphine.
- Methadone has no active neurotoxic metabolites, unlike morphine and hydromorphone.
- Methadone is metabolized in the liver, not by glucuronidation, but by the cytochrome P450 group of enzymes which explains some of the interaction seen with methadone and not with other opioids.
- 60% of methadone is eliminated through non-renal routes, mainly the fecal route.
- Urine pH will impact excretion: pH > 6, renal clearance 4% of methadone, pH < 6, renal clearance 30% of methadone.
- Liver or renal disease does not significantly impact the pharmacokinetics of methadone.
- Methadone is very lipophilic.
- It is rapidly distributed in tissues and released slowly from extravascular sites resulting in slow elimination and a prolonged half-life.
- Methadone produces analgesic activity within about an hour after oral administration. Initially, the duration of action is four to six hours much like other potent opioids. However, with chronic dosing, the drug will accumulate and, if administration continues every four to six hours, significant toxicity can occur.
- The half-life of methadone can vary widely from a few hours to more than 100 hours.
- Like other potent opioids, there is wide variability from patient to patient in the pharmacokinetics of methadone.

Routes of administration

- In Canada, only the oral form of methadone is available as available as tablets (1mg, 5mg, 10mg, 25mg), as a solution (10mg/ml), or as a powder that can be reconstituted in liquid form in a variety of concentrations.
- Parenteral methadone can be made from the powder, but subcutaneous administration can be associated with local reactions.
- Rectal administration of methadone can be very effective thanks to the highly lipophilic nature of the drug.

Drug or agents	Interaction effects
Antidepressants	
Tricyclic antidepressants	↑ levels of tricyclics
SSRI drugs	↑ methadone levels
Antivirals	
Zidovudine (AZT)	↑ zidovudine levels
Ritonavir	↓ methadone levels
Antifungals	
Ketoconazole	↑ methadone levels
Fluconazole	↑ methadone levels
Anticonvulsants	
Phenytoin	↓ methadone levels
Carbamazepine	↓ methadone levels
Gabapentin	no effect
Phenobarbital	↓ methadone levels
Antibiotics	
Rifampin	↓ methadone levels
Ciprofloxacin	↑ methadone levels
Clarithromycin	↑ methadone levels
Erythromycin	↑ methadone levels
Isoniazid	↑ methadone levels
Benzodiazepines	Accentuates the respiratory depression and sedation
Neuroleptics	
Risperidone	↓ methadone levels
Cardiac drugs	
Quinidine	↑ methadone levels
Verapamil	↑ methadone levels
Spironolactone	↓ methadone levels
Gastrointestinal agents	
Cimetidine	↑ methadone levels
Somatostatin	↓ methadone levels
Other agents	
Cannabinoids	Accentuates analgesia (animal studies)
Grapefruit juice	↑ methadone levels
Acute alcohol ingestion	↑ methadone levels
Chronic alcohol ingestion	↓ methadone levels
Smoking	↓ methadone levels

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Methadone for cancer pain: An analgesic with a difference

Supported by an education grant from Pharmascience

Methadone interactions

Because of the involvement of the cytochrome P450 enzyme pathway in metabolizing methadone, drugs and other agents that impact that pathway will therefore affect the metabolism and therefore the pharmacokinetics of methadone.

Side effects of methadone

Methadone has a similar spectrum of side effects to other potent opioids, but there are some differences in prevalence of these side effects. Side effects seem to be less, perhaps related to the highly lipophilic nature of the drug:

- Constipation and nausea seem to be less
- Sedation seems to be less
- Hallucinations are rare
- Myoclonus is less frequent.

One of the rare, but potentially dangerous side effects of methadone is QT interval prolongation and Torsades de Pointes. This usually occurs with high doses of methadone, but drug interactions as described above that increase methadone concentrations may contribute to this.

Obviously, the most dangerous side effect is respiratory depression that was seen much more commonly when the opioid equivalency of single dose methadone was used to calculate chronic dosing.

Dose equivalency of methadone and morphine

Initially, methadone equivalency as expressed in opioid equivalency tables was that 8 mg of methadone was equivalent to 10 mg of morphine. For the pharmacokinetic reasons expressed above, clinicians quickly discovered that, with chronic dosing, methadone was 10 to 20 times more potent than morphine.

When to consider methadone for analgesia

1. Severe complex or neuropathic pain that is not responding to other opioids and adjuvants.
2. Suspicion of opioid tolerance as evidenced by very high doses of opioids.
3. Severe and intractable opioid side effects.
4. Renal impairment or significant liver impairment.

When NOT to consider methadone for analgesia

1. A prescriber who is inexperienced in using opioids and methadone.
2. Limited follow-up of patients or limited accessibility of the prescriber.
3. Non-compliant patients.
4. Drug abuse.

Methadone should only be prescribed by a physician who is aware of its pharmacokinetic and pharmacodynamic properties and who has experience in its use.

If you are not experienced in using methadone, enlist the help of a pain expert.

Methadone dosing

1. Individualize and titrate: patients on low-dose opioid may require a ratio of 1:5, on high-dose 1:20 (methadone/morphine equivalent).
2. 1:10 is most common starting.
3. 1:20 is appropriate starting ratio for elderly patients.
4. For patients on high-dose opioids, greater than 1000 mg morphine equivalent/day 50 mg methadone is upper limit per dose at inception of therapy.
5. Begin dosing at eight-hour intervals.

Morphine to methadone conversion

There are a number of methods for converting from an opioid to methadone. On an outpatient basis, I would recommend:

Day 1	Start 5 to 10 mg methadone every eight hours.** Decrease the other opioid by 1/3. Wait three days to judge initial stabilization. Use other opioid for breakthrough
Day 4	Depending on response, increase methadone by 10 mg each dose. Decrease the other opioid further by 1/3. Allow 5 to 10 mg methadone q4-6h PRN for breakthrough
Day 7	Depending on response, increase the methadone. Stop the other opioid. Use methadone for breakthrough.

***Methadone can be administered q12h

Patients should be cautioned to report increasing sedation immediately to their physician.

Methadone licence

In Canada, a methadone "licence", actually an "exemption", is required to prescribe methadone for analgesia under the Controlled Drugs and Substances Act. An application must be made to the Office of Controlled Substances and an application form for exemption must be completed. The letter of application must state that the physician has had some education or experience in using methadone and that a physician mentor with experience in using methadone is available. Support from the provincial medical licensing body may be required.

The website is: **www.hc-sc.gc.ca/hecs-sesc/ocs/health/methadone.htm**

References are available. Contact Dr. Librach by e-mail at **larry.librach@utoronto.ca**.