From the guest editor’s desk

By Charles Hayter, MA, MD, FRCPC

There has been much interest in the use of bisphosphonates for bone metastases in recent years, and there is now a great deal of published literature on this subject. In this issue of Hot Spot, we are pleased to have contributions from three experts in this field. On this page, Dr. Rebecca Wong provides an introductory overview and in the insert, Drs. Scott Berry and Mark Clemons review their use in prostate and breast cancer. We hope that these contributions help to clarify your understanding of the use of bisphosphonates in metastatic cancer.

Elsewhere in this issue, you will find a timely article by Ms. Karen Faith about the impact of SARS on the health care team, and an excellent approach to the management of anger in cancer patients by Dr. Mary Vachon. In the research corner, Drs. Jackson Wu and Edward Chow highlight the new multi-centre trial of re-irradiation for painful bone metastases. My own contribution focuses on the career of Dr. Herbert Bruce, a pioneer of cancer control in Ontario.

Happy reading and a pleasant spring!

Bisphosphonates in cancer

By Rebecca Wong,
MB, ChB, MSc, FRCPC

Bisphosphonates are structural analogues of pyrophosphates which act through multiple mechanisms to provide physicochemical protection for normal bone against cancer cells. The use of bisphosphonates for the management of bone metastases started with their use in the management of malignant hypercalcaemia in the 1980s, and they were rapidly adopted as part of standard management for this condition. Almost at the same time, the first randomized trials on the use of bisphosphonates for the more general treatment of bone metastases were conducted. Since then, over 50 randomized trials on bisphosphonates and bone metastases have been published. The objectives for which bisphosphonates are being tested are: 1) to delay the onset of bone metastases (in patients with no evidence of bone metastases); 2) to delay the development of skeletal-related complications; and 3) for the treatment of specific complications of bone metastases, namely pain and hypercalcaemia.

In this issue of Hot Spot, Drs. Clemons and Berry provide a state-of-the-art summary of the indications for bisphosphonates in the management of bone metastases in the two most common cancers, breast and prostate. In a landmark article in 1998 by the Cancer Care Ontario Provincial Guidelines Initiative (CCOPGI), the role of bisphosphonates in breast cancer patients with bone metastases was systematically reviewed. The data was updated recently in 2002 and other similar work, including a Cochrane review on this topic, has been published. Based on 16 randomized controlled trials (RCT), bisphosphonates can reduce and delay skeletal complications including bone pain and the need for radiation therapy, and preserve quality of life. The relative risk for skeletal-related events (SRE) (excluding hypercalcaemia) on bisphosphonates was 0.88 (95% CI 0.81-0.96). Since the first systematic reviews on the topic, bisphosphonates have become part of standard therapy for patients diagnosed with bone metastases from breast cancer. Unknown questions include when to discontinue the use of bisphosphonates when disease progresses, and the switching of bisphosphonates in the presence of bony disease progression.

continued on page 2...

In this issue: Bisphosphonates in cancer; Anger in the person with advanced disease; Ethics and SARS: Collateral damage and relationships in health care; Historical Vignette: Dr. Herbert Bruce; Ontario cancer visionary; Research Corner.

Insert - Bisphosphonates in hormone-refractive prostate cancer and breast cancer
Anger in the person with advanced disease

By Mary L.S. Vachon, RN, PhD

One of the more difficult issues to deal with in the care of those with advanced disease is the patient or family member who is angry. While understanding intellectually that anger can be a normal response to advancing disease, caregivers often find themselves responding at an emotional level and meeting the patient’s anger with their own anger, or avoiding the patient as a way of not having to deal with uncomfortable emotions.

Depression is often viewed as anger turned in on the self, but Tavris (1989) suggests that anger might be depression turned outward: “follow the trail of anger inward and there you will find the small still voice of pain”. Anger can also reflect underlying fear. Some other underlying causes of anger might include: the individual’s pre-existing personality; a response to illness-related issues e.g. delayed diagnosis, lack of information, concerns about treatment; issues other than the illness e.g. family or financial issues; a spiritual crisis; unrealized ambition, often accompanied by guilt; loss of control; a feeling that there is no escape; or depression (Faulkner, Maguire & Regnard, 1994).

Faulkner et al. provide a helpful algorithm for dealing with anger (below).

**Reference**

Mary Vachon, RN, PhD, is a psychotherapist in private practice. She can be reached at maryvachon@sympatico.ca.

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**Part 1: Initial Approach**

<table>
<thead>
<tr>
<th>IS PERSON CONTROLLED AND CONTAINED?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARE YOU PICKING UP PASSIVE ANGER?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

- Acknowledge what anger does to you – if it always makes you angry or irritable during the interview, it would be sensible to ask another person to conduct the interview.
- NB. It is often impossible to choose where anger is expressed.

**Supportive Counselling**

- Acknowledge anger (e.g. I can see this has made you angry)
- Negotiate to discuss cause (e.g. can you explain to me why you are feeling like this?)
- Encourage expression of anger (e.g. just how angry have you been?)
- Avoid the temptation to defend yourself or others

**Part 2: Management**

<table>
<thead>
<tr>
<th>IS THE ANGER MISDIRECTED?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS THE ANGER ESCALATING?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>IS THE PERSON REFUSING TO ACCEPT LIMITS?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

- Pathological anger - Withdraw from interview immediately
- NB. It is often impossible to choose where anger is expressed

**IS ANGER PERSISTING?**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

- Check if there are other reasons unconnected with the illness.
- Explore if this is part of normal behaviour for the person (e.g. I get the feeling you are easily upset)

**IS THE PERSON APATHETIC, OR EXPRESSING FEELINGS OF HOPELESSNESS?**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

- Exclude depression
- Go to Part 2

**IS ANGER CAUSING ISOLATION?**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

- Confront and acknowledge their isolation (e.g. Your anger seems to have left you feeling lonely)
- Explore the effects of the isolation on relationships

**Bisphosphonates, continued from page 1...**

Evidence around the role of bisphosphonates in prostate cancer matured only in more recent years. Dr. Berry, the primary author for the CCOPGI on the role of bisphosphonates in prostate cancer, provided a systematic review on this topic. Based on nine RCTs, with the largest trial examining the role of zoledronate acid, the data is in support, with an 8% absolute reduction in SRE. The official release of this guideline will provide important evidence to guide clinical practice.

In addition to these two most common cancers, bisphosphonates have an established role in clinical practice in multiple myeloma. Their role in delaying SRE from other primaries such as lung cancer remains undefined, however. Finally, their effectiveness as a pain relief therapy for patients with painful bone metastases has been systematically reviewed and published as a Cochrane review in 1992 and, more recently, updated and published in collaboration with the Canadian Coordinating Office for Health Technology Assessment (Wong, Shukla, Mensinkai & Wiffen, 2004). In this review, based on 51 RCTs, the authors concluded that bisphosphonates do have effectiveness in providing pain relief in patients with bone metastases, and can be a useful adjunct in patients with multiple sites of pain, that are difficult to control with simple analgesics and radiotherapy.

In summary, bisphosphonates do have a definite role in the management of bone metastases. Their optimal use requires careful consideration of patient and disease factors in addition to coordination with other treatment modalities. This issue’s insert by Drs. Berry and Clemons provides a convenient reference for the state-of-the-art in this topic for today’s busy clinicians.

**Reference**

March 2004 marks the first anniversary of the beginning of the SARS crisis in Ontario. This past year has given public health organizations an opportunity to consider some global responsibilities and, in particular, the need for interdependence in the promotion of worldwide public health interests. Since the outbreak of SARS, many in the field of bioethics have reflected on some of the ethical considerations raised by SARS in health care. One article explored 10 key ethical values that figured prominently during the crisis. A summary of these ethical values included: individual liberty; protecting the public; proportionality of measures taken and risks faced; reciprocity; transparency; privacy; protection from stigmatization; duty to care; equity and solidarity (Singer, Benatar, Bernstein et al., 2003). This article, along with others, discussed areas of collateral damage resulting from the emergence of SARS and the subsequent crisis in its wake (Bernstein & Hawryluck, 2003; Gastin, Bayer & Fairchild, 2003; Hall, Angus, O’Brien-Pallas, Wynn & Donner, 2003). Examples of collateral damage included the impact of quarantine on health professionals, patients and their family members, inpatients who were not visited due to restrictions, and the inability at times for nursing staff to provide optimum levels of patient care and contact due to infection control measures.

Although it may be stretching the conventional meaning of collateral damage, I propose that relationships also sustained collateral damage. Why are relationships in health care and possible collateral damage to them of any ethical importance? The basis of one’s professional obligations to provide care and to fulfil one’s duty to patients is to be in a specific relationship with them. Ethics is concerned with how we govern those relationships. The act of caring for others is a basic moral obligation for us all as human beings, as administrators, and as health care professionals. As Levine stated: “to care in this sense, means to be troubled about the troubles of others” (Levine, 1987). Furthermore, hospitals are moral communities, influenced by the way institutional values are experienced on a daily basis between people, within relationships of co-workers, supervisors, and administrators. Therefore, any impact on these relationships is of ethical concern, as sustaining relationships is fundamental to providing care, and to the hospital as a moral community.

During the height of infectious disease containment measures, there were enormously frustrating barriers in providing care to patients. This was particularly felt in the area of cancer care. Collateral damage was witnessed whenever oncology physicians or clinical staff could not visit with dying patients, or when outpatient could not access their regular clinic visits or chemotherapy appointments. This form of collateral damage led one author to conclude: “The SARS crisis in Toronto hospitals was one such socio-historical moment that represented an extraordinary interruption of the foundations of patient care activities” (Hall, Angus, O’Brien-Pallas, Wynn & Donner).

Relationships between health care institutions and health care workers were affected when an outbreak of SARS resulted from what was perceived as inadequate infection control measures and/or poor communication. Trust within working relationships was compromised when co-workers did not comply with infection control standards. Hospital and staff relations were strained by the uncertainty of risks posed to staff, the long shifts they performed, as well as the restrictions placed upon them. Health care workers faced the sad reality that many of the seriously ill and fallen were colleagues from their own or other hospitals. All of these variables were unfolding within a larger context of dealing with a previously unknown illness, a media frenzy of changing information, and a spectre of mistrust.

However, relationships did not only sustain collateral damage. Relationships within health care were also enhanced through this crisis. Stories of heroism, solidarity, and altruism actually deepened relationships. Hospitals caring for SARS patients pooled resources, personnel, and expertise. Many health care professionals who cared for SARS patients forged close relationships with their patients as well as...
New NCIC CTG Study (SC 20) – Re-Irradiation of painful bone metastases

Radiation therapy relieves pain in approximately 70% of patients with painful bone metastases. According to several randomized trials, the duration of pain relief is between 12 and 24 weeks. Because of persistent pain (i.e. no response to initial radiotherapy), or recurrent pain (i.e. response to initial radiotherapy but pain relapses), up to 30% of patients would be given repeat radiation (i.e. re-irradiation).

However, the efficacy of re-irradiation has not been well-documented among the major clinical trials of bone pain management by radiotherapy. Retrospective reviews did suggest that repeat radiotherapy was efficacious in 50 to 90% of cases, particularly for patients who had a good response to the initial radiation. Some patients who did not respond to initial radiation benefited from re-irradiation. Clinically important questions to investigate are: How well does re-irradiation work? and, What is the optimal dose fractionation in re-irradiation?

The SC 20 is a National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG) led intergroup study with collaborators from the United Kingdom (Dr. Peter Hoskin), the Netherlands (Dr. Yvette van der Linden), and Australia/New Zealand (Dr. Daniel Roos). The aim of the study is to determine: (1) the efficacy of re-irradiation, and (2) whether re-irradiation given as a single fraction (one treatment) is any less effective than a series of five (or eight) fractions. The total dose of radiation given in five fractions is higher than a single fraction. The trial design is shown in Figure One.

This study will also evaluate potential factors that may help predict which subgroup of patients is least responsive to palliative radiotherapy. A companion study involves collection of urine samples for biochemical markers of bone turnover. In one study of 20 patients, the level of these markers was shown to correlate with pain response to radiotherapy. The ability to select patients who are intrinsically unresponsive to radiotherapy will help avoid unnecessary treatment and encourage the consideration or investigation of other treatment alternatives (e.g. vertebroplasty, thermal ablation) for these patients.

SC 20 has been activated in five centres in Canada, including TSRCC (Dr. Edward Chow), PMH (Drs. Andrea Bezjak and Rebecca Wong), Juravinski Cancer Centre (Hamilton – Dr. William McMillan), Northwestern Ontario Regional Cancer Centre (Thunder Bay – Dr. Conrad Falkson), and Tom Baker Cancer Centre (Calgary – Dr. Jackson Wu). More Canadian centres are expected to participate.

Please support this Canadian intergroup study to answer questions that are clinically relevant and biologically informative. If your patient has an area of bone pain (spine, pelvis, extremity) that was previously treated with radiation, and the pain persists or recurs, consider referring the patient back to the radiation oncologist for evaluation.

For more information about SC 20 or the companion urinary markers study SC 20U, please contact Dr. Jackson Wu, e-mail: jacksonw@cancerboard.ab.ca, or Dr. Edward Chow, Edward.Chow@sw.ca.

Dr. Jackson Wu, (SC 20 Study Canadian Co-chair), Department of Oncology, Tom Baker Cancer Centre, Calgary, Alberta. Dr. Edward Chow, (SC 20 Study Chair), Department of Radiation Oncology, Toronto Sunnybrook Regional Cancer Centre, Toronto, ON.

Figure One

<table>
<thead>
<tr>
<th>Initial RT Dose</th>
<th>Pain recurs or persists</th>
<th>Stratify</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-8 Gy/1# or 20 Gy/5# or 24 Gy/6# or 30 Gy/10# (extremity metastases only)</td>
<td>≥ four weeks from first treatment</td>
<td>1. Treatment centre</td>
</tr>
<tr>
<td>** 20 Gy/8#/1.5 weeks for spine or whole pelvis that was initially treated with 20 Gy/5# or 24 Gy/6#**</td>
<td></td>
<td>2. Initial RT dose (single vs. multiple)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Response to initial RT (responder vs. non-responder)</td>
</tr>
</tbody>
</table>

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References available on request.
Use of bisphosphonates in men with hormone refractory prostate cancer

By Scott Berry, BSc, MD, MHSc, FRCPC, Division of Medical Oncology, Toronto-Sunnybrook Regional Cancer Centre and University of Toronto

Background

- Prostate cancer is the most frequently diagnosed cancer in Ontario - it is the fourth most common cause of cancer death in Ontario and the third most common cause of cancer death in men.
- Bone metastases occur in up to 75% of men with prostate cancer and produce significant morbidity including pain, pathologic fractures, and spinal cord compression.
- Prostate cancer responds well to androgen ablation therapy, but eventually progresses; therapies for “hormone-refractory prostate cancer” (HRPC) remain limited.
- The use of bisphosphonates has been most extensively studied in men with HRPC and bone metastases.

Bisphosphonates for HRPC – An overview

- While prostatic bone lesions are predominantly osteoblastic, increased osteoclast activity and bone resorption play a major role in the skeletal morbidity of prostate cancer.
- Evidence on the use of bisphosphonates in hormone-refractory prostate cancer is limited to eight randomized trials examining five different bisphosphonates in different patient populations. Five of these trials were small, including less than 100 patients (See Table One for summary of the randomized trials).

- In contrast to other disease sites where bisphosphonates have been more extensively evaluated, it is difficult to derive treatment recommendations for bisphosphonates as a class of agents for HRPC in light of the limited available evidence. Therefore, treatment recommendations must be made for specific bisphosphonates in specific clinical situations.

Bisphosphonates for reducing skeletal-related events (SREs)

For the population of men studied in Saad’s trial (men with HRPC and minimally symptomatic bone metastases) it is reasonable to consider zoledronic acid (4 mg intravenously every three weeks) to reduce SREs.
- Zoledronic acid is associated with an 8% absolute reduction (from 44% to 36%) in SREs.
- The palliative benefits of reducing SREs in these men should be considered in light of:
  - zoledronic acid’s toxicities (fatigue, anemia, myalgia, fever, and lower limb edema) that were increased in the zoledronic acid arm of the trial at a rate comparable to the reduction of SREs.
  - the fact that zoledronic acid showed minimal effect on pain prevention, and neutral effect on overall quality of life.

Bisphosphonates for pain reduction

- None of the major randomized trials have shown a statistically significant benefit of any bisphosphonate in terms of treating bone-related pain.
- For the clodronate trials:
  - Two (Ernst, Strang) were positive for subgroup analyses of men with moderate pain.
  - Three trials (Kylmäla, Strang, Elomaa) showed non-significant trends for clodronate providing better pain relief.
  - Three trials (Kylmäla, Strang, Elomaa) showed non-significant trends for clodronate providing better pain relief.

Table One: Randomized trials of bisphosphonates in hormone-refractory prostate cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Bisphosphonate</th>
<th>1° Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith (1989)</td>
<td>57</td>
<td>Etidronate</td>
<td>Pain reduction</td>
</tr>
<tr>
<td>Elomaa (1992)</td>
<td>75</td>
<td>Clodronate (Chemo: Estramustine)</td>
<td>Pain reduction</td>
</tr>
<tr>
<td>Kylmäla (1997)</td>
<td>57</td>
<td>Clodronate (Chemo: Estramustine)</td>
<td>Pain reduction</td>
</tr>
<tr>
<td>Strang (1997)</td>
<td>55</td>
<td>Clodronate</td>
<td>Pain reduction</td>
</tr>
<tr>
<td>Ernst (2003)</td>
<td>209</td>
<td>Clodronate (Chemo: Mitoxantrone)</td>
<td>Pain reduction</td>
</tr>
<tr>
<td>Dahut (2001)</td>
<td>52</td>
<td>Alendronate</td>
<td>PSA response</td>
</tr>
<tr>
<td>Small (2003)</td>
<td>350</td>
<td>Pamidronate</td>
<td>Pain reduction</td>
</tr>
<tr>
<td>Saad (2002)</td>
<td>643</td>
<td>Zoledronic acid</td>
<td>Skeletal-related events</td>
</tr>
</tbody>
</table>

BOTTOM LINE:

Although the subgroup analyses involved a small number of patients, all of the clodronate trials showed some trend indicating that clodronate could improve pain. Clodronate could be considered as an adjunct to other palliative therapies (i.e., chemotherapy, radiotherapy) for reducing pain, along with traditional measures for pain management.

Duration of bisphosphonates

- The optimal duration of bisphosphonate treatment in men with hormone-refractory prostate cancer has not been evaluated in randomized trials.

Summary and future directions

- Zoledronic acid has been shown to reduce SREs in men with minimally symptomatic HRPC, but it does have toxicities. The risks and benefits of zoledronic acid should be discussed with individuals so they can make informed decisions about whether they would like to receive the medication.
- Although there are some suggestions that clodronate may be useful in reducing pain in men with HRPC, well-designed studies of bisphosphonates need to be designed to more definitively determine their role in palliating pain.

Table Two: Skeletal-Related Events (SREs)

- Pathological fracture
- Vertebral fracture
- Non-vertebral fracture
- Spinal cord compression (SCC)
- Radiation therapy to bone
- Surgery to bone
- Change of antineoplastic therapy for bone pain

Supplement to Hot Spot, the newsletter of the Rapid Response Radiotherapy Program of Toronto Sunnybrook Regional Cancer Centre - May 2004
Use of bisphosphonates in women with breast cancer

By Mark Clemons, MB.BS, MRCP (London),
MSc, MD (Manchester)
Division of Medical Oncology,
Toronto-Sunnybrook Regional Cancer Centre
and University of Toronto

Background

- Over 5,000 Canadian women died of breast cancer in 2003.
- Bone metastases (BM) are the initial site of recurrence in 35 to 40% of patients and eventually occur in 60 to 80% of patients with metastatic disease.
- BM have consequences for patients in terms of morbidity and mortality.
- Morbidity: two-thirds of patients with BM will develop skeletal-related events (SREs).
- Prognosis: women with bone-only or bone-dominant disease have median survival of 19 to 25 months. However, patients with SREs, such as pathological fractures, SCC, or hypercalcemia, have a shorter median survival, of 12, four and three months respectively.

The bisphosphonates

- Bisphosphonates (BPs) are potent inhibitors of osteoclast-mediated bone resorption.
- Most commonly used BPs in Canada are intravenous pamidronate (90 mg every three to four weeks), oral clodronate (1.6 g/day) and intravenous zoledronic acid (4 mg every three to four weeks).
- BPs have confirmed benefit for management of hypercalcemia of malignancy.
- In patients with BM and pain, BP may be a useful adjunct to conventional measures for pain control (Wong & Wiffen, 2002).
- For women with metastatic breast cancer who have plain radiograph or a CT scan evidence of lytic destruction of bone, BPs in addition to chemotherapy or hormonal therapy can significantly reduce and delay skeletal complications including bone pain, quality of life, and the need for radiation therapy (Hillner et al., 2003; Pavlakis & Stockler, 2002).
- The beneficial role of BPs on skeletal morbidity for metastatic cancers is time-dependent and no reduction in SREs is reported until at least six months on a BP (Ross et al., 2003). These findings have two implications:
  - BP should probably be started when BM are diagnosed
  - In patients asymptomatic from BMs with a very poor prognosis (due to, for example, the presence of extensive visceral metastases) a more efficient strategy may be to delay initiation of BP or avoid it altogether.

Which is the best bisphosphonate?

- There are few randomized comparisons of the efficacy of the different BPs.
- Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia with a higher complete response rate and improved time to treatment response.
- A randomized trial comparing zoledronic acid and pamidronate for the treatment of cancer-related bone lesions in patients with multiple myeloma or breast cancer showed that zoledronic acid was equivalent to pamidronate with respect to the primary efficacy variable (the proportion of patients who experienced a SRE, not including hypercalcemia). A multiple event analysis of patients with breast cancer who received zoledronic acid showed a significant reduction in the risk of developing skeletal complications compared with patients who received pamidronate.

The bisphosphonates – useful agents, but not panaceas

- BPs have radically improved the management of BM from breast cancer. But these agents are not panaceas.
- The management of BM is best performed within a multidisciplinary framework. All disciplines have a role to play and none should be considered superior to any other.
- BPs are expensive agents.
- Toxicity – BPs are usually well tolerated but can be associated with gastrointestinal side effects, renal adverse effects, phlebitis, arthralgias, pyrexia, electrolyte disturbances, and hypocalcemia. Uveitis is a rare complication of treatment with pamidronate.
- The necessity for repeat clinic visits for pamidronate and zoledronic acid infusions is costly both financially (additional costs such as nursing time and infusion apparatus) and in terms of patient time for monthly hospital visits.

Stopping bisphosphonates

- Practice guidelines state that BP therapy should be initiated at the time of diagnosis of BM. They rarely discuss whether or not they should be stopped after further bone progression while on BP therapy (Hillner et al., 2003).
- There is no evidence from clinical trials that address the optimal duration of BP use.

Conclusion

- The management of patients with BM will continue to be a major therapeutic challenge.
- The use of BPs for BM has led to a major improvement in the management of women with metastatic breast cancer.

References


