PHOTODYNAMIC THERAPY FOR BONE METASTASES

An avenue for earlier identification and treatment

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The treatment of bony metastases is a multidisciplinary endeavor. In settings such as The Bone Metastases Clinic at Toronto Sunnybrook Regional Cancer Centre, integration of the efforts of palliative care specialists, radiation oncologists and orthopedic surgeons has furnished a patient-focused environment to guide decisions about applying currently available therapies to treat symptomatic bone metastases.1,2

Further input by medical oncologists and other allied health professionals (e.g. from nursing, occupational therapy, psychology, nutrition, social work) gauges patients’ functional limitations, home environment and overall health condition. This enables the team to balance the available options and choose those that will have the most impact on pain relief and quality of life, at acceptable levels of risk.

EXISTING TREATMENTS

Analgesic pain titration is critically important and often the first step. For treating symptomatic bony lesions with low risk for pathologic fracture and related complications, the use of splints, orthoses, assistive devices for walking and modifications to the home environment are important and very helpful.

Destructive bony lesions of the vertebral column and weight-bearing long bones often pose significant risk of pathologic fracture. Spine fractures entail issues of pain, instability, deformity and spinal cord compression with resultant paralysis. Pathologic fractures of weight-bearing long bones pose significant morbidity because of their impact on ambulatory capacity. Local therapies for vertebral metastases include external beam radiation therapy and a variety of surgical options — often directed towards skeletal stability and pain relief — ranging from newer minimally...
invasive surgical (MIS) strategies to more conventional decompressive and stabilization surgery. Currently available local treatments have limitations. Certain neoplasms are relatively radioresistant. Further, complications such as radiation enteritis and myelopathy limit the amount of radiation that can be locally directed. Rates of major wound complications are higher in people who have had prior local radiation therapy: in spinal surgery they are 3- to 4-fold greater. Minimally invasive surgical approaches such as vertebroplasty can provide significant pain relief in acute pathologic vertebral body fracture. While helping improve stability, however, such an approach does not address any biologic aspects of tumour growth — it adds nothing to tip the balance between tumour growth and host bony repair in favour of repair and skeletal stability. An important general orthopedic principle is that any surgical fixation device used for fracture will eventually fail from repetitive cyclic loading unless bony healing occurs.

**Toward improved treatments**

With growing numbers of patients affected by bony metastases, research aiming to develop efficacious local therapies with minimal side effects and low associated patient morbidity is needed. New therapies should be directed both at ablating the local tumour and enhancing bony stability, likely favouring a multimodality therapeutic approach. The most promising strategy is early identification of clinically significant, precritical bone metastatic lesions followed by early institution of treatment.

**PHOTODYNAMIC THERAPY BASICS**

Photodynamic therapy (PDT) is a promising cancer treatment that induces localized tumour destruction by the photochemical generation of cytotoxic singlet oxygen. PDT employs wavelength-specific light combined with a photosensitizing agent. Photosensitizing agents are delivered to the tissues orally, intravenously or by slow-release injection (depot). The drug accumulates in neoplastic cells and is activated by light at low power without causing thermal effects. Subsequent generation of toxic oxygen-free radicals leads to oxidative stress, damaging plasma and intracellular membranes and eliciting direct local tumour cell death. The effective treatment size is governed by characteristics of the light (energy) delivered to the tissue, level of tissue oxy-

degeneration and the tissue’s optical properties. Longer light typically penetrates deeper into tissues than does light of shorter wavelength. Two main parameters govern selective targeting of tumour while preserving normal adjacent tissue:

- certain photosensitizers preferentially accumulate within tumour cells as compared to normal, nonmalignant cells
- photodynamic reactions occur only in tissues that contain adequate photosensitizer drug and that are exposed to light of the correct wavelength

In vivo studies in human breast cancer cell lines have provided evidence supporting PDT efficacy in eliciting tumour cell death. Clinically, PDT has achieved encouraging early results in treating breast cancer recurrences and other primary malignancies.

**ACCESSING BONE BY MIS**

Minimally invasive surgical strategies are at the forefront of current research and clinical use in treating a variety of medical conditions, including orthopedic disorders, and are associated with reduced surgical morbidity. Endoscopic-guided spinal surgery is used to treat adult deformity and degenerative spinal conditions, and recent reports describe MIS in routine surgical lumbar decompression and instrumentation (rod insertion). Vertebroplasty, used clinically to treat painful osteoporotic spinal compression fractures and spinal metastases, is gaining increasing acceptance and use. This minimally invasive local technique employs percutaneous fluoroscopic placement of a spinal needle or trocar into the vertebral body to allow direct injection of polymethylmethacrylate (PMMA, i.e. bone cement) to mechanically stabilize the vertebra. It can afford significant pain relief in patients with pathologic and osteoporotic vertebral fractures, and has become an important adjunct in the treatment of painful vertebral metastases. More recently, a few centres have used a similar technique — cementoplasty — to treat periacetabular bony metastases. Adapting MIS techniques to access bone allows placement of optical fibres adjacent to osteolytic lesions. Preclinical research is underway on the feasibility and potential of photodynamic therapy to treat bone metastases, as well as on other local adjuvant treatments including laser and radioablation.

**PDT VIA VERTEBROPLASTY**

Knowledge regarding the use of PDT to treat structural bone lesions is currently limited. A key challenge is delivering light to the target location. To address this issue in vertebral metastases, our research group has adapted the MIS technique of vertebroplasty to apply PDT: percutaneous fluoroscopy guides placement of small-diameter optical fibres adjacent to affected vertebrae. A variety of murine and rodent models of bone metastases are available to evaluate novel local therapies. Initial feasibility and efficacy studies on the use of PDT to treat vertebral metastases were supported by a Canadian Breast Cancer Research Alliance (formerly Canadian Breast Cancer Research Initiative) IDEA grant, which is a type of grant supporting small-scale pilot studies or investigations of concepts. In vivo bioluminescent reporter imaging (a molecular imaging technique that labels tumour cells with an optical
marker, then noninvasively monitors cell proliferation using photon detection) in an animal model using human breast carcinoma cells demonstrated the efficacy of a single percutaneous treatment of PDT to elicit significant reduction in local tumour growth in vertebral metastasis.29

**Remaining issues**

While initial feasibility studies have solved technical concerns regarding implantation of optical fibres to target specific vertebrae, critical issues remain, chiefly involving light and drug dosimetry to closely define the therapeutic window of safety and efficacy. Ongoing funding by the Canadian Breast Cancer Foundation’s Ontario Chapter has been integral to this work.

The choice of ideal initial photosensitizing drugs requires further study. Several agents with minimal systemic side effect profiles are available. BPD-MA (benzoporphyrin-derivative monoacid A) is a photosensitizer that can be used to target either the neovasculature (which provides essential nutrients to the cells) or the cells directly, depending on the drug–light interval. Its absorption spectrum is stimulated by a longer wavelength of light, possibly desirable to achieve greater depth penetration. BPD-MA used clinically for ocular macular degeneration has demonstrated minimal systemic side effects.27,28 ALA (5-aminolevulinic acid, a prodruk that leads to endogenous synthesis of the photosensitizer protoporphyrin IX, [PpIX]) has the potential for high tumour-to-neural tissue selectivity — an important consideration for applications in areas near the spinal cord.

Understanding of the optical properties of light transmission and attenuation in human bone is limited, so requires ongoing in vivo study.29,30 Preliminary safety of PDT in non-tumorous porcine lumbar spine has been demonstrated and planning is underway for multicentre preclinical studies to evaluate PDT efficacy in structurally larger bone lesions.31

**PROMISING OUTLOOK**

PDT poses an interesting potential adjunct for local treatment of bone metastases. There are no known contraindications to the use of PDT pre- or post-radiation or surgery. Unlike radiotherapy — where there are limits to the amount of spinal irradiation that can be administered, and where wound complications following subsequent conventional spinal surgery are a significant problem — no limits are anticipated on the number of PDT treatments that can be administered, once the correct light and drug dosimetry is determined. Further, PDT can potentially be applied to radioresistant tumours. Given its potential biologic benefits on tumour growth kinetics, PDT could be used as a neo-adjuvant treatment just prior to PMMA injections given in vertebroplasty to mechanically stabilize metastatically involved vertebrae. The selectivity of PDT in being able to locally target cancer cells is particularly appealing in the spine, where conservation of healthy neural tissue of the spinal cord is critical.

More study is needed on the potential need for fractionated treatments. A practical solution may be percutaneous implantation of an optical fibre that can be left in situ, as in brachytherapy. Such a transdisciplinary approach encompassing tumour biology and minimally invasive surgical strategies will likely provide important future adjuncts to patient palliation.

**References**


continued on page 12
justified — arguing that pharmacokinetic monitoring of oral busulfan could provide equivalent outcomes. The monitoring, however, is expensive and inconvenient.

This study provides the most compelling evidence to date that IV busulfan is significantly less toxic than the oral agent, particularly with respect to veno-occlusive disease. As the cost of treating even a single case of this condition is substantial, the use of IV busulfan could well be justified in terms of cost alone — let alone the improvements in clinical outcomes seen in this study. It would be interesting to know longer-term outcomes, particularly regarding graft-versus-host disease, transplant-related mortality, relapse and overall survival. There is some evidence that exposure to busulfan within the desired range may result in less acute graft-versus-host disease and it would be interesting to know whether such was the case in this study. Given the dramatic differences in early mortality it is very likely that outcomes in the longer term will also be better — but this needs confirmation. The current evidence for the superiority of IV busulfan is such that randomized controlled studies probably will not be carried out. We already know that drug exposures within an acceptable range are achieved much more often when the drug is given intravenously compared to orally.

Many important questions about this preparation remain, however. Preliminary evidence indicates that administering higher IV doses less frequently than 4 times daily and combining busulfan with other agents such as fludarabine instead of cyclophosphamide may improve tolerability and convenience without compromising efficacy. Studies similar to the one carried out by CIBMTR could establish this with more confidence.

In addition we do not know whether the desired therapeutic range of exposure established for oral busulfan is necessarily appropriate for the IV form, particularly when combined with other agents. While the question of superiority of intravenous busulfan has been definitively settled, it will be some time before we have solid answers to some of these other questions.

### Table 2. Selected outcomes in patients receiving IV vs oral busulfan as pre-transplant conditioning

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