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Spinal metastasis subjected to photodynamic therapy: an update

W Jerjes[1,2]*, HB Tan[1], C Hopper[2], P Giannoudis[1]

Abstract

Introduction

This is a review of the evidence on the use of photodynamic therapy in the management of bone lesions in spinal metastasis. The literature was searched for relevant articles and the results were examined. The search included on-going trials that aim to tackle this disease. Eight studies were identified in the literature; none were applied on humans.

Conclusion

All studies reached the conclusion that photodynamic therapy is an effective modality in managing osteoblastic and/or osteolytic spinal bone metastasis. Evidence regarding the efficacy of this therapy suggests that it will have a leading role in interventional hard tissue oncology and thus we propose a technique for managing such pathology.

Introduction

Spinal metastasis

Tumour metastasis to the spine is not uncommon. It is the third most common site for tumours to metastasize, after the lungs and liver. Up to 70% of cancer patients (at autopsy) have spinal metastasis, but only 10% become symptomatic. Spread is usually via arterial route, although direct invasion through intervertebral formina and retrograde spread via Batson's plexus have been previously described. Vertebral body and epidural space metastasis is more common than intramedullary and intramural ones. Two-thirds of the lesions are localized at the anterior portion of the vertebral body[1–4].

Primary sources of the disease have been mainly identified in the lungs and breast. Spinal metastasis have also been known to result from other primary pathologies like gastrointestinal, kidney and prostate malignancies, lymphoma, melanoma and multiple myeloma[1,3].

Over two-thirds of the lesions are identified in the thoracic area (T4–T7), one-fifth in the lumbar region and remaining in the cervical spine. However, more than half of the patients have lesions at multiple levels. Along with the mass effect, axonal destruction and demyelination result following cord distortion. Venous infarction and haemorrhage result from vasogenic oedema and venous congestion; the effects of vascular compromise[1–4].

Nearly all patients with symptomatic disease experience bone and/or back pain. Sensory disturbances, radiculopathy, motor dysfunction and bladder and bowel involvement have been reported in half of the symptomatic cases[1–6].

Radiological investigations include plain X-rays to identify vertebral body and pedicles erosions (i.e. owl-eye erosion of the pedicles indicating metastatic disease), which become identifiable when 30%–50% of the bone is destroyed. Computed tomographic imaging helps to assess the integrity of the vertebral column, while magnetic resonance imaging (MRI) is the modality of choice, especially when neurological abnormalities are manifested. Bone single photon emission computed tomography (SPECT) and positron emission tomography (PET) are modalities that may enable guiding the management of spinal disease[2,3,4].

Current interventions

To date, no treatment for this unforgiving disease has proven to be effective in improving life expectancy; median survival in symptomatic patients with spinal metastasis does not exceed 12 months. Patient's quality of life is known to slightly improve after conventional interventions, easing the symptoms caused by bowel or bladder involvement as well as the pain[1,3,4,6].

Therefore, it is fair to say that pain control and functional preservation are the main aims of any management. The efficacy of an intervention is usually judged through several functional scoring systems. Choosing between different interventions can be challenging and is usually judged by the patient's presenting symptoms (i.e. pain related to bone destruction, pathological fractures or stretching of the periosteum, while vertebral compression and/or collapse causes axial pain), ability to function at the time of presentation (i.e. ability to ambulate is a favourable prognostic sign) and psychological status[1,3,4,5,6].

At present, radiotherapy remains the gold standard treatment for this disease. Meanwhile, surgery is usually employed for patients with bony collapse and/or acute neurological problems. Pain is primarily managed with steroids and non-steroidal anti-inflammatory drugs, while neuropathic

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pain is managed with anti-epileptics. Radiotherapy can be effective in controlling bone metastasis pain[1–4].

Photodynamic therapy (PDT)

PDT remains an elegant therapeutic option in interventional oncology. In principle, light application to the target 'lesional' area leads to a photochemical reaction. This is usually induced several hours after the administration of the photosensitizer and leads to selective injury to the target tissue. The efficacy of the treatment depends on the type and concentration of the photosensitizer, light dose, dose rate, availability of oxygen and cellular localisation. The treatment can be repeated with minimal cumulative toxicity[7–9].

Two generations of photosensitizer are currently used in oncology. Porfimer sodium (Photofrin, first generation) is commonly used in Barrett's high-grade dysplasia, cervical, gastric, oesophageal, endobronchial and papillary bladder cancers. Using this haematoporphyrin, a maximum absorption can be reached at 630 nm with a drug dose of 2 mg/kg and a drug light interval of 48–72 h, fluence of 100–200 J/cm^2 and fluence rate of 10 mW/cm^2. Aminolevulinic acid (5-ALA), a natural haem precursor, has been successfully applied in basal cell carcinoma, actinic keratosis and oral dysplasia. With the formation of protoporphyrin IX, a maximum absorption can be reached at 635 nm. The drug can be given topically in a 20% paste or systemically (oral 60 mg/kg or intravenous 30 mg/kg). The drug light interval is 36 h, with fluence of 100 J/cm^2 and fluence rate of 100–150 mW/cm^2.[7–9]

mTHPC (Foscan, second generation), a more forceful photosensitizer for cancer management, when compared with Photofrin and 5-ALA, is commonly used in advanced head and neck cancer. The maximum absorption is at 652 nm with a drug dose of 0.05–0.15 mg/kg and drug light interval of 96 h, fluence of 10–20 J/cm^2 and fluence rate of 100 mW/cm^2. Third generation photosensitizers (tin ethyl etiopurpurin, mono-L-aspartylchlorin-e6, benzoporphyrin derivative and lutetium texaphyrin) are already in clinical trials; initial results showed better tumour specificity and shorter generalised photosensitivity[7–9].

Amphinex, a new generation of photosensitizers, is used to initiate the photochemical internalisation process with a selected chemotherapeutic agent (i.e. bleomycin). Preliminary results of an on-going clinical trial suggests that patients with advanced sarcomas, squamous cell carcinomas and ductal carcinomas showed complete response of all target lesions after this therapy. Amphinex is usually given about 93 h before a slow bleomycin infusion and subsequent illumination with a diode laser to initiate photochemical internalisation[10].

Delivery of PDT

Targeting tumour tissue occurs through different means. Direct targeting followed by initiation of necrotic or apoptotic sequence has been described (i.e. singlet oxygen generated by a photochemical reaction). In addition, targeting the tumour vasculature (i.e. intimal hyperplasia) and starving the tumour can lead to the same effect, which is followed by initiation of an immune response against the residual pathological tissue[7–9].

Light delivery modus operandi differs depending on tumour type. Treatment of surface or superficial tumour lesions is performed through surface illumination. This is a very successful method and the depth of effect can reach up to 1 cm when using certain photosensitizers [i.e. meso-tetrahydroxyphenylchlorin (mTHPC)]. Superficial bulky tumours can be surgically reduced and the photochemical reaction can be applied to the base to eradicate involved tumour margins[7–9].

Difficulty arises when treating deep invading tumours. Here, special needles need to be inserted into the target tissue and fibres are fed through to deliver the light. Initial management involves preoperative imaging to determine size and depth, followed by reconstruction of multihole grids to allow needle insertion and fibre loading, enabling light delivery to the deep margins. Fibres need to protrude by 2–3 mm from the needle tip to allow maximal tissue illumination. Subsequently, each single unit (needle and fibre) is pulled back to ensure light delivery to the whole tumour volume in two-dimensional application therapy[7–9].

Intra-operative image-guided needle insertion into the tumour mass has enabled more accurate identification of the tumour centre and periphery. Here, a three-dimensional application therapy is enabled. This is usually aided by a specialist in interventional radiology. To date, guiding modalities include two-dimensional ultrasound, MRI, computed tomography (CT), nasoendoscopy, laryngoscopy and bronchoscopy[7–9].

When the photosensitizer is activated by light, it is expected that the photochemical reaction will last for a few hours. However, subsequent tumour death may continue to show macroscopic changes up to 6–8 weeks after light delivery. This usually appears macroscopically as a layer or mass of necrotic tissue separated from surrounding living tissue followed by tissue regeneration. Healing usually occurs with minimal scarring. There is sparing of tissue architecture, providing a matrix for the regeneration of normal tissue[7–9].

We aimed to review the literature on the use of PDT in the management of bone lesions in spinal metastasis.

Materials and methods

The literature was searched for spinal metastatic cancer articles. The main search engines were PubMed and Medline.

The keywords used in the search included: 'photodynamic therapy and bone', 'photodynamic therapy and

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bone disease', 'photodynamic therapy and bone pathology', 'photodynamic therapy and hard tissue', 'photodynamic therapy and bone disorders', 'photodynamic therapy and bone tumour', 'photodynamic therapy and bone cancer', 'photodynamic therapy and sarcoma', 'photodynamic therapy and spine', 'photodynamic therapy and spinal disease', 'photodynamic therapy and spinal tumour', 'photodynamic therapy and spinal cancer' and 'photodynamic therapy and spinal metastasis'.

Although the main aim of this study was to highlight the advances in the management of spinal metastasis using PDT, we widened the research criteria to ensure that all the relevant articles were included.

Results

Published studies

Eight published studies were identified when searching the English literature for the last 20 years (Table 1). The first reported use of PDT for the treatment of metastatic lesions in bone was described by Burch et al. in 2005. Benzoporphyrin derivative-monoacid-mediated PDT was used

Table 1 Review of the currently published studies

Authors[ref.]	Year published	Study location	Materials	Methods	Assessment methods	Study results
Hojjat et al.[18]	2011	Canada	Rat spinal motion segments with osteolytic metastases	PDT + BPs	Intensity-based 3D image registration technique	It was possible to quantify the positive mechanical effects of combined BP + PDT treatment in the metastatic spine
Wise-Milestone et al.[17]	2011	Canada	Rat model of mixed osteolytic/osteoblastic spinal metastases	PDT	Mechanically testing or histological processing	PDT was shown to significantly decrease tumour burden and osteoclastic activity, thereby improving vertebral bone structural properties
Won et al.[15]	2010	Canada	Healthy rat model	PDT	Micro-CT stereological analysis and axial compression testing	PDT may improve vertebral mechanical stability
Won et al.[16]	2010	Canada	Rat model of human breast carcinoma	PDT ± BPs	Micro-CT and histological processing	PDT ablated malignant tissue and improved the structural integrity of vertebral bone. Combined treatment further enhanced bone architecture and strength
Akens et al.[13]	2010	Canada	Rat model of human breast carcinoma	PDT	Post-treatment bioluminescence, histomorphometric assessment and neurologic evaluation	Safe and effective drug-light dose combination and applied light energy was identified
Akens et al.[14]	2007	Canada	Rat model of human breast carcinoma	PDT	Fluorescence spectrophotometry to assess photosensitizer tissue concentration	The highest ratio for BPD-MA concentration was found 15 min after injection, which can be recommended for therapy in this model
Burch et al.[11]	2005	Canada	Rat and porcine models with spinal metastasis	PDT	Bioluminescent signal and histological analyses	Results support the application of PDT to the treatment of primary or metastatic lesions within bone
Burch et al.[12]	2005	Canada	Rat model of human breast carcinoma	PDT	Histologic and immunohistochemical analysis	Ablative effect on vertebral metastases

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to target lesions within the spine and appendicular bone in rats and porcine models. Histological examination[11] of vertebrae 48 h post-PDT revealed a necrotic radius of 0.6 cm with an average fluence rate of 4.3 mW/cm^2.

In the same year, the same group used the photosensitizer benzoporphyrin-derivative monoacid ring A (BPD-MA) in rat models. The effect varied in proportion to light energy, with the greatest anti-tumour effect observed at 150 J using a 3 h drug-light interval. Nine of 22 rodents during the 3 h drug-light interval developed hind limb paralysis following treatment, consistent with drug uptake studies demonstrating an increase in spinal cord uptake 3 h following drug administration. The observation of paralysis following treatment highlights the importance of closely defining the therapeutic window of treatment in safety and efficacy[12].

Following this, Akens et al. aimed to test two photosensitisers, BPD-MA- and 5-ALA-induced protoporphyrin IX (PpIX), for their potential use to treat bony metastases. In contrast to BPD-MA, ALA-PpIX did not demonstrate an appreciable difference in the uptake ratio in tumour-bearing vertebrae compared with spinal cord. The highest ratio for BPD-MA concentration was found 15 min after injection, which was recommended for therapy in this model[13]. The same group defined the therapeutic window of vertebral PDT in a murine pre-clinical model of breast cancer metastasis using BPD-MA. A safe and effective drug-light dose combination in this model appeared to be 0.5 mg/kg BPD-MA and applied light energy of less than 50 J for the thoracic spine and 1.0 mg/kg and 75J for the lumbar spine. For translation to clinical use, it is an advantage that BPD-MA, a second-generation photosensitizer, is already approved to treat age-related macular degeneration[14].

Won et al. investigated the effects of PDT on the structural integrity of vertebral bone in healthy rats. A single PDT treatment was administered to healthy Wistar rats at photosensitizer and light doses known to be effective in athymic rats bearing human breast cancer metastases. Not only was PDT successful in ablating metastatic tumour tissue in the spine, but the positive effects of PDT on bone suggested that PDT may also improve vertebral mechanical stability[15]. Another study, by the same group, treated athymic rats with bisphosphonates (BPs) and PDT and found it to further enhance bone architecture and strength in both metastatically involved and healthy bone[16].

A recent study assessed the effect of PDT on mixed osteolytic/osteoblastic spinal metastases. The overall bone quality resulting from these lesions consisted of decreased structural properties but without a significant reduction in mechanical integrity. PDT was shown to significantly decrease tumour burden and osteoclastic activity, thereby improving vertebral bone structural properties. While non-tumour-bearing vertebrae exhibited significantly more new bone formation following PDT, the already heightened level of new bone formation in the mixed tumour-bearing vertebrae was not further increased. As such, the effect of PDT on mixed metastases may be more influenced by suppression of osteoclastic resorption as opposed to the triggering of new bone formation[15]. This study was followed by an evaluation of the effects of combined BP and PDT on bone strain in metastatic vertebrae using image registration, which showed the positive mechanical effects of combined BP + PDT treatment in metastatic spine[16].

On-going work

The first prospective Phase I clinical trial is currently taking place at the Sunnybrook Health Sciences Centre, University of Toronto. Patients eligible for the study include individuals with vertebral disease, where vertebroplasty/kyphoplasty and minimally invasive surgical techniques are an option to help in restoring spinal stability. The aim will be to ablate spinal metastasis and later stabilize the spine through vertebral osteoplasty, thereby optimizing the quality of life and providing an effective treatment.

How to do it

The patient is usually discussed at the multidisciplinary team meeting. The photosensitizer is usually administered at a specific dose (mg/kg) intravenously into the mid-cubital vein at a specific drug-light interval (hours) before treatment. This would allow the agent to accumulate in the pathological area, thereby increasing its efficacy. Patients are usually kept in a side-room (with dimmed lighting) to avoid systemic photosensitisation.

Intra-operatively, CT is used to examine the pathological tissue (centre and periphery). The main aim here is to determine tumour volume, depth and invasion of vascular structures. This is usually followed by insertion of 70 mm long 18 gauge spinal needles under image guidance into the pathological tissue. A path into the bone (vertebrae) needs to be prepared prior to needle insertion. Great care is taken to ensure that the needles are inserted parallel to each other with a specific distance in between (judged by the photosensitizer in use). If the treatment is close to a major blood vessel, a safety distance is implemented to avoid any possible risk to promoting rupture, in case the vessel wall contains a tumour.

Diode laser is used for illumination. Bare polished-tip laser-light delivery fibres with a core diameter of 400 mm are introduced through the spinal needles into the tumour. The fibres are allowed to protrude by 2–3 mm from the needle tip into the tissue to ensure maximal tissue illumination. Light is then delivered from the fibres to the target tissue at a specific energy (J/cm^2) per site. Each bare-tip fibre delivers a specific output power (Watts).

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Any residual pathological tissue in between the necrotic areas is also expected to die from damage after oxygen deprivation. However, overlapping treatment fields are clinically insignificant, as illumination of the area is adequate to activate the non-thermal photochemical process. Thick tumours are treated with pull-back technique (of the needle and fibre) at each time to ensure illumination of the whole tumour volume.

An iso-illumination treatment plan is carefully implemented and supervised by a senior physicist to ensure adequate light delivery to all suspect areas, with minimal overlapping between the fields of treatment using a grid system. Measurements are made with regard to the distribution of the light fluence rate, optical properties, drug concentration and tissue oxygenation for PDT. The position of the pulse oximeter is changed every 30 min to avoid any skin burn or nail damage that would result from photochemical reaction by red light (660 nm). Post-operatively, gradual light re-exposure and regular neurological assessments are implemented.

Patients are discharged from hospital care when appropriate. Six weeks post-operatively, re-staging MRI or CT views, where appropriate, are acquired to assess outcome. Patients are asked to report on the outcome of their therapy in terms of symptom relief and improvement of function. A post-operative clinical assessment is reported by the treating clinician at the first post-PDT review (at 4–6 weeks). A post-operative radiological assessment is reported by the same interventional radiologist.

Challenges

- Light transmission through bone:
  - Previous evidence from animal models has shown that light travels within tumour-involved bone with minimal obstruction from the surrounding cortical bone. In fact, non-involved cortical bone may act as a barrier to prevent light travelling to the spinal cord[11–19].
- Delivery of light to the target tissue:
  - As the treated tissue is hard and interstitial application is a necessity, a path into the pathological area need to be prepared prior to needle and subsequent light fibre insertion. Care must be taken to avoid tumour seeding while preparing such a path[11–19].
- PDT effect on tumour growth kinetics:
  - Evidence from animal models using bioluminescence imaging showed positive effect. Burch et al. suggested that the imaging represent evidence of cellular metabolism, and the intensity depends on the energy status of the cell and reflects the availability of ATP and molecular oxygen within the cell. The applicability to diseased and normal human tissue is still unknown. It was possible to demonstrate that low intensity laser irradiation can play an important role in promoting biostimulation of osteoblast cell cultures. Therefore, whether biostimulation of osteoblastic cell cultures by PDT or the cytotoxic effect of this therapy occurs only depends upon the light dose, and the results can be completely variable[11–19].
- Cervical stability in humans after PDT:
  - Depending on the photosensitizer used and light properties, PDT may or may not cause significant bone damage. When applied to the spine, this could lead to instability and crush injuries leading to devastating results. Animal studies using specific photosensitizers and light parameters suggest that PDT can provide mechanical stability to the spine. Spinal stabilisation procedure may be required prior to PDT, especially when treating multi-level or extensive disease[11–19].
- Potential damage to the spinal cord and/or peripheral vascular structures:
  - PDT is a cold photochemical reaction and is unlikely to cause damage to nerves; however, the use of inappropriate photosensitizer dose and light energy may cause injuries[11–19].
- Two-dimensional image-guidance technology in treatment of three-dimensional disease:
  - Important considerations such as the disease margin or host–tumour interface are significant factors in the eventual outcome. To ensure a more logical and complete PDT treatment, a tumour volume and slightly larger treatment volume should be considered. This is aided by the use of computer modelling, a needle grid (to ensure parallel iso-doses of illumination) and timed illumination of fibres. The great utility of this treatment modality is not only its repeatability (unlike radiotherapy), but the accuracy of treatment (to avoid unwanted bystander tissue damage, again unlike radiotherapy)[11–19].
- Post-operative pain:
  - Post-operatively (post-PDT), patients experience a considerable amount of pain in the treated area, which can augment an ongoing pain. The pain post-PDT usually peaks at 48–72 h. Special PDT pain protocols are followed. The standard regimen involves a fentanyl transdermal patch for 72 h at 12 mg/h with morphine sulphate (immediate release), as required for breakthrough pain. Dose escalating the patient's own pain medication or prescribing patient-controlled analgesics is implemented when indicated. Usually, different specialist centres have different PDT pain control protocols depending on experience and the areas treated. The pain from spinal metastasis is complex as it involves bone

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pain, neuropathic and radicular pain[11–19].

- Residual photosensitivity:
  - Photosensitivity represents a problem as the skin continues to be sensitive to light for few weeks, sometimes for 13 weeks with some photosensitizers. Gradual light re-exposure at an incremental rate of specific lux per day is implemented. Every patient is instructed on the need to avoid direct sun exposure for a specific period of time after injection and is given light exposure guidelines. Sometimes, patients fail to achieve a gradual re-exposure to sunlight. As a result, they develop a skin burn (first or second degree) when they are exposed for the first time to direct sunlight. In addition, the skin over the injection site (especially the arm area) is more sensitive to light and skin burn; this has been reported to occur for up to 10 weeks after photosensitisation in this area[11–19].
- Collateral damage:
  - Adjacent macroscopically normal appearing tissue can become photosensitised and undergo necrosis or apoptosis, causing an unfavourable outcome (i.e. skin necrosis). The optimal way of reducing these effects is by ensuring that the light does not illuminate any adjacent areas, either by using special probes or by shielding the adjacent tissues[11–19].

Discussion

 authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies. The application of this 'Cinderella' modality has been successful in the management of several cancers in-cluding head and neck, skin, brain, lung, pancreas, intra-peritoneal, breast and prostate. In addition, PDT was proven to be extremely success-ful in treating vascular anomalies.

It is fundamental to the success of PDT that tumour margins are accessed and illuminated and the depth of necrosis is greater than the depth of each individual tumour (adequate treatment margin). In in-terstitial PDT, imaging can simply guide the optical fibres to the ap-propriate disease volume, which can be co-registered with a treatment volume allowing accurate assess-ment of delivered treatment doses. Image guidance also allows the guid-ance of delivery apparatus away from vital structures that may not have been otherwise palpable, i.e. arteries and nerves. It also ensures the parallel placement of delivery needles, enabling improved dosage administration profiles because the surface orientation of the needles is not a reliable measure of their deeper course, which may have been distorted by changes in tissue con-sistency or architecture (i.e. bone, tendons).

A multi-disciplinary team of surgeons/physicians trained in PDT, medical physicists and interventional radiologists) working together is essential to the efficient modern management of deep-seated disease, especially with end-stage or locally advanced dis-ease. The concept of disease treatment has evolved and imp-ortant considerations such as disease margin or hosttumour interface are a significant factor in the eventual outcome. PDT is well tolerated and effective especially for end-stage carcinomas, sarcomas and vascular anomalies.

It is expected that response and outcome will vary between different pathologies, depending on the structure, volume and severity of the pathology. Additionally, it is worth acknowledging that for the same grade of the same disease, there is variability in patients' responses to PDT.

Image-guided PDT is slowly gaining acceptance in the treatment of many 'end-stage' or otherwise 'untreatable conditions'. Furthermore, unlike radiotherapy, it can be applied multiple times with overlapping treatment fields. This added therapeutic 'manoeuvring room' provides patients with more options and as demonstrated by the data, an im-proved quality of life.

The drawback of image-guided PDT is that it requires some extra equipment and training, neither of which is exorbitant when compared with the capital outlay of surgery or radiotherapy, with their associated complications, which would have been avoided by the use of this technology. The advantage of the technique is that PDT is now delivered to a target volume (which represents the disease volume with a margin of normal tissue) and can be mapped. It also means that PDT has evolved from depending upon just surface illumination to a modality that can now be used to treat deeper-seated lesions.

Conclusion

In summary, the growing body of evidence regarding the efficacy of PDT suggests that it will have a leading role in interventional hard tissue oncology, especially when managing spinal metastatic disease.

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