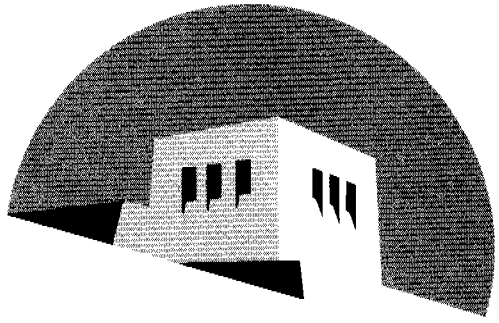

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Clinical and Pharmacoeconomic Considerations in the Treatment of Bone Metastases

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CLINICAL AND PHARMACOECONOMIC CONSIDERATIONS IN THE TREATMENT OF BONE METASTASES

STATEMENT OF OBJECTIVES

The primary goal of this lesson is to present the reader with information on the different types of therapy that are available for the treatment of bone pain due to metastatic disease and the cost effectiveness of each. This lesson will concentrate on various radiopharmaceuticals, bisphosphonates, surgery, radiation therapy, and pharmaceuticals that are available for pain control. An analysis of the effectiveness, cost, and side effects of each modality will also be presented.

Upon successful completion of this material, the reader should be able to:

1. List the seven radiopharmaceuticals that are available as approved agents or are currently in clinical trials for the palliation of bone pain due to metastases.
2. List six other techniques that are available for the palliation of bone pain due to metastases.
3. Describe the effectiveness of all of the techniques listed for the control of bone pain due to metastases.
4. Describe the side effects of all of the techniques listed for the control of bone pain due to metastases.
5. Estimate the cost associated with each of the techniques listed for the control of bone pain due to metastases.
6. Compare the use and cost of each modality in the control of bone pain due to metastases.

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INTRODUCTION

Control of pain caused by metastases of primary cancers is an important clinical challenge. It has been estimated that 75% to 90% of patients with advanced cancer experience chronic pain.[1] The prevalence of this problem is costly not only in monetary terms but also patient quality of life. As our understanding of and clinical experience with the treatment of pain expands, it becomes more difficult for clinicians to select optimal therapy from the growing array of treatments available. Options currently available for the palliation of pain due to metastatic spread of osseous cancer include radiopharmaceuticals, external beam radiotherapy, chemotherapy and surgery, analgesics and bisphosphonates.

These therapies should be individualized based on patient need and clinician experience. For optimal therapy, it is necessary for the clinician and the patient to consider clinical, humanistic and economic issues. Historically, only clinical efficacy and toxicity were incorporated into the therapy selection process, but more recently it has been recognized that patient quality of life needs and cost restraints must also be considered. Definition of optimal pain therapy is elusive because of the lack of outcome studies directly comparing the previously listed treatment alternatives. Because of the lack of these studies, pharmacoeconomic comparisons of available treatments are difficult. There are a few investigations,[2,3] which attempt to compare the palliative characteristics of radiopharmaceuticals versus external beam radiotherapy in their ability to decrease the use of analgesics and opiates. Even less information is available concerning the ability of bisphosphonates to reduce patient use of pain medication.[4] There are no studies that compare the palliative efficacy of bisphosphonates with radiopharmaceuticals.

Because of the lack of comparative information about treatment alternatives, this lesson will provide a review of current literature on palliative approaches for painful metastatic bone disease including a review of effectiveness, side effects, and cost. By providing this information, the reader should be able to consider economic as well as clinical issues in their decision-making.

RADIOPHARMACEUTICALS FOR PALLIATION OF BONE PAIN

This section is intended to provide an overview of all of the agents that are approved in either Phase I, II, or III trials, or are in a research and development phase. A review article on many of these drugs by McEwan[5]

provides some excellent information. This continuing education lesson will update McEwan's paper as well as present information on the pharma-coeconomic analysis of these agents compared to other forms of pain palliation.

Strontium-89 Chloride (Metastron®)

The use of ^{89}Strontium Chloride ($^{89}SrCl_2$) for the treatment of metastatic bone disease and the pain associated with it dates back to the early 1940s.[6] Strontium-89 has several characteristics that make it useful for the treatment of bone pain caused by the spread of certain cancers. These characteristics are summarized as follows. Strontium-89 is in the same chemical family as calcium, thus it will form strontium hydroxyapetite crystals that are incorporated directly into the bone matrix. Strontium-89 as strontium chloride is produced on a nuclear reactor by the following reaction: $^{88}Sr(n^0,\gamma)^{89}Sr$. and decays with a physical half-life of 50 days. The maximum energy of the beta particle emitted is about 1.4 MeV. Since ^{89}Sr has very poor imaging characteristics, it has been proven by the use of ^{85}Sr that strontium isotopes concentrate in metastatic bone sites for long periods of time, while they clear rapidly form normal tissue.[7]

In June of 1993 the FDA approved Metastron® for use as a palliative agent in the management of bone pain due to metastases from either prostrate or breast cancer. Because of its ability to concentrate in metastatic cancer of the bone for long periods of time, ^{89}Sr has been shown to be very effective at relieving pain associated with metastases from either breast or prostate cancer.[8-10] According to Robinson and associates[8] approximately 50% of the injected dose of ^{89}Sr concentrates in the bone. After 14 days the ^{89}Sr has cleared normal bone and all of the remaining drug is associated with metastatic sites. Since Metastron® is concentrated in all metastatic bone sites, it has been proven to be as effective as hemibody radiation for pain control. According to Quilty and associates,[11] Metastron® is much more effective at preventing the occurrence of new disease. More recent trials[9,10] in Europe have shown that pain relief of some magnitude has been obtained in as high as 90% of the patients treated. These trials have not only shown effectiveness, but they confirm the drug can be safely given repeatedly every 3 months with only transient hematologic side effects.

A standardized procedural guideline for the treatment of bone pain with ^{89}Sr has been available since 1996.[12] When these guidelines are followed closely, the adverse effects associated with this therapy are minimal in most cases. The most common adverse effect is the "flare" response. This response is due to sudden swelling of the tumor from the radiation and usually occurs within the first week to 10 days following treatment and is commonly associated with less extensive metastatic disease. The "flare" response can cause an increase in pain for the first week to 10 days and should not be mistaken as a worsening of the disease. Patients should be informed of this potential reaction. The second most frequent side effect is a transient lowering of marrow production. This side effect is most commonly seen at 3-4 weeks post therapy with a rebound at 2-3 months. If patients are on chemotherapy or other types of marrow depressing agents, then the platelet and white cell counts should be monitored closely as transfusion may be necessary. The most

severe risk factor is disseminated intravascular coagulation (DIC), which may occur due to post therapy thrombocytopenia. There have been reports of death occurring from DIC associated with the use of beta emitting radiopharmaceuticals,[12] however, DIC is a recognized complication of advanced prostate cancer and its association with ^{89}Sr administration may be coincidental.

Metastron® is available from Nycomed Amersham. The drug is shipped in 4 mCi/4mL lots that expire 28 days post calibration. The cost of the drug ranges from $2500.00 to $2900.00 per vial, depending on whether it is purchased directly from Nycomed Amersham in Chicago or if it is supplied by a centralized nuclear pharmacy. The most common dose given to the patient is 4 mCi, however a dose of 40-60 uCi/kg can be given depending on the weight of the patient.

Samarium-153 Ethylenediamine-tetramethylene Phosphonic Acid (Quadramet®)

Samariium-153 Ethylenediamine-tetramethylene Phosphonic Acid (^{153}Sm-EDTMP), or Quadramet®, is an FDA approved drug indicated for use in pain relief in patients with confirmed osteoblastic metastatic bone lesions that enhance on a radionuclide bone scan.[13] Samarium-153 has a physical half-life of 46 hours and emits both a gamma ray and multiple beta particles. The 103 keV gamma emission has an abundance of 28% and can be imaged with any standard gamma camera. Although it emits multiple beta particles, the maximum beta energy for ^{153}Sm is 810 keV. Production of the isotope is accomplished by irradiation of a $^{152}Sm0_3$ target with neutrons from a nuclear reactor. The equation for production is $^{152}Sm(n^0,\gamma)^{153}Sm$. The final product is produced by reacting $^{153}Sm0_3$ with Ca/Na EDTMP in 0.1N HCl. The molar ratio of 153Sm to EDTMP is 1:1, thus forming a very stable complex. The mechanism of uptake for ^{153}Sm-EDTMP is very similar to the ^{99m}Tc phosphonates used in diagnostic bone imaging. The EDTMP portion of the molecule will bind to the hydroxyapetite crystal of the bone matrix by passive chemabsorption. This uptake is reversible thus allowing the drug to passively diffuse from the bone matrix. According to the literature [14] an average of 52% of the injected dose remains in the skeletal system at 6 hours with the remainder being eliminated in the urine. Quadramet® is known to concentrate in metastatic bone sites more than in normal bone, thus delivering a much higher radiation dose to tumor cells than to normal bone tissue.

Unlike Metastron®, the literature does not contain information comparing Quadramet® with other forms of pain relief such as radiation therapy. Because of a lack of comparison, one can only assume that ^{153}Sm-EDTMP is similar to ^{89}Sr in its ability to control bone pain and prevent the spread of disease when compared to radiation therapy and other modalities. There are a number of articles[15-19] that have been published regarding dosage and dose/response to Quadramet,® which would seem to imply that it has the ability to control pain as well as ^{89}Sr. According to these articles, the response rate for pain control varies from 55% when patients receive 0.5 mCi/kg body weight[14] to 95%[16] in patients receiving up to 1.5mCi/kg body weight. The average percent of patients that receive some degree of pain relief was about 80% which is comparable to results obtained with ^{89}Sr. Several of the above

references compared pain relief based on the activity of Quadramet® that was given. Doses ranged from 0.5 mCi/kg body weight up to 3.0 mCi/kg body weight. A dose of ^{153}Sm-EDTMP equivalent to 1.0 mCi/kg body weight generally appeared to provide the best pain relief with a smaller percentage of patients having hematologic side effects.

Although Quadramet® and Metastron® appear to have similar response rates, some differences are worth noting. First of all, Quadramet® is approved for use in a wider variety of metastatic bone tumors based on evidence of favorable response to the drug.[16-19] The demonstration that metastases from tumors other than breast or prostate respond well to ^{153}Sm EDTMP may be due to the relatively short physical half-life of the ^{153}Sm. A much larger radiation dose in a very short period of time can be delivered with ^{153}Sm when compared to ^{89}Sr which means that highly metabolic tumors may respond better to the short lived nuclide. The second note of interest is that, according to both Serafini[17] and Resche,[18] patients with breast cancer statistically responded better to Quadramet® than patients with other types of diseases including prostate cancer. No reason for the increased response was given. The final note of interest is that the average duration of relief of pain for ^{153}Sm EDTMP is only 6-8 weeks compared to 10 - 12 weeks for ^{89}Sr. This difference may be due to the fact that the above published reports on Quadramet® treatment groups include metastatic sites from many different types of cancers rather than just breast or prostate cancers. One can speculate that tumors that metastasize more aggressively may require treatment more frequently than others.

Although published guidelines[12] for treatment of metastatic bone pain refer only to Metastron®, the product insert for Quadramet® contains guidelines for its use. The guidelines for the use of either Quadramet® or Metastron® are similar. As is the case with ^{89}Sr, a common side effect experienced by patients receiving ^{153}Sm EDTMP is a "flare" response. Most patients receiving Quadramet® will experience a lowering of marrow production with the nadir occurring at 2-3 weeks post injection. The rebound by the marrow will be complete in 6-8 weeks as compared to 8-12 weeks for ^{89}Sr.

Currently, the distribution of Quadramet® in the United States is handled by Berlex Laboratories of Wayne, New Jersey. The drug can also be obtained through a central nuclear pharmacy. Samarium-153 EDTMP is shipped frozen and expires 8 hours post thaw. The recommended treatment dose is 1 mCi/kg body weight. The cost of Quadramet® is $2200.00 for any mCi amount of drug that is ordered if it is purchased directly from Berlex. The cost may vary if it is purchased through a central nuclear pharmacy. Because of the expense of the drug, if it is ordered and not opened the drug may be returned to Berlex with no expense to your institution.

Phosphorous-32 Sodium Phosphates

Like ^{89}Sr, phosphorus-32 sodium phosphate (^{32}P-NaH_2PO_4) has been used for palliative bone pain relief since the early 1940s.[20] Phosphorus-32 was the first radionuclide to be approved by the FDA for use in the palliation of bone pain due to metastatic disease. Production of ^{32}P is accomplished on a nuclear reactor according to the equation $^{32}S(n^0,\gamma)^{32}P$. The physical half-life of the

radionuclide is 14 days. Phosporus-32 decays by beta emission with a maximum energy of 1.71 MeV. Since ^{32}P has no gamma emissions, one cannot obtain images for biodistribution purposes. Bone matrix consists mainly as a combination of calcium, phosphorous and oxygen, so ^{32}P is readily incorporated into the bone. Unfortunately, phosphorous, being an essential element of the body is also incorporated into other organs as well as bone. The maximum uptake of ^{32}P in bone does not occur until 3 days following injection, and at 2 weeks about 33% of the injected dose remains in the bone with an additional 20% remaining in soft tissue.[21] According to the product insert, ^{32}P is approved for use in the treatment of polycythemia vera as well as palliation of bone pain caused by metastases of certain types of cancer. Interestingly, the type of primary cancers or the fact that the metastases must be imageable on a diagnostic bone scan are not part of the indication for use of this drug. The lack of the above information in the product insert is most likely due to "grandfathering" of ^{32}P for use in palliation of pain due to metastases of cancer to the bone.

The use of ^{32}P sodium phosphate for the treatment of pain caused by metastases to the bone is well documented in the literature.[21-26] Historically, ^{32}P has typically been used in combination with surgery or some form of drug therapy[21-25] and a placebo controlled trial has never been reported.[21] A recent article[26] compared ^{32}P directly with ^{89}Sr for control of pain from metastases to the bone. Exactly why no one has studied ^{32}P alone for its ability to control bone pain from metastases is unclear. According to the aforementioned literature, ^{32}P is very effective at treating pain when used either in combination with surgery, with other drugs, or when used alone. According to Nair,[26] ^{32}P was just as effective as ^{89}Sr for palliation of bone pain with a response rate of 88% for ^{32}P as compared to 93% for ^{89}Sr. These results are slightly higher than those obtained by others,[21] but Nair's article was based on a small patient population.

The guidelines for use of ^{32}P as a palliation agent would be similar to those for ^{89}Sr as previously referenced. A more serious side effect of ^{32}P use is hematologic depression. Like both Metastron® and Quadramet®, ^{32}P has been shown to cause a transient drop in WBC and platelet counts.[21,26] This change is statistically more severe with ^{32}P than has been reported for other radiopharmaceuticals[26] and deserves special attention. A very close observation of platelet and WBC counts (weekly) is warranted. Not only is the marrow production lowered significantly with ^{32}P as compared to other radiopharmaceuticals, but also the time required for rebound of the platelets and WBC counts is longer. For Metastron® and Quadramet® the recovery time is about 6-12 weeks as compared to as long as 6 months for ^{32}P. Higher rates of patient transfusions have been reported[21] using ^{32}P than with other radiopharmaceuticals, although the necessity for these has been questioned.

Reports of dosing trials using ^{32}P have produced, at best, conflicting information. Maxfield[27] reported in 1958 that ^{32}P should only be given in small multiple doses over a period of time in order to avoid severe hematologic depression of the bone marrow. By using this technique, doses of up to 20 mCi of ^{32}P could be administered without causing more than transient effects on

the marrow production. These results confirmed an earlier study by Albright.[28] More recently[21, 26] it has been reported that a single injection dose of up to 12 mCi can be given safely with only transient marrow effects. As is the case with other bone pain palliation agents, an increase in dose does not seem to have a significant effect on as pain relief.

The manufacturer of phosphorus-32 sodium phosphate is Mallinckrodt Medical in St. Louis, MO. It is sold in 5 mCi lots at a cost of approximately $400.00, if purchased directly from the manufacturer. Expiration is 6 weeks from calibration. This cost is considerably less than either Metastron® or Quadramet® and is likely the reason why there is still a great deal of interest in using ^{32}P today.

Rhenium-186 hydroxyethylene Diphosphonate (^{186}Re HEDP)

A review of the periodic chart of the elements indicates that rhenium is in the same family as technetium. Since much of the diagnostic imaging in nuclear medicine uses ^{99m}Tc, it would be reasonable to assume that any radiopharmaceutical labeled with ^{99m}Tc could also be labeled with rhenium. Such is the case with the bone-seeking agent ^{186}Re-HEDP. Rhenium-186 is produced on a nuclear reactor from pure rhenium metal by the reaction: $^{185}Re(n^0\gamma)^{186}Re$. Once the ^{186}Re is obtained, it is oxidized to perrhenate ion which is then reacted with a combination of stannous chloride and Na_2H_2HEDP to form the desired product. This is the same reaction as is used in the kit production of ^{99m}Tc-HEDP, except the formation of ^{186}Re-HEDP requires heating at 100°C for 10 minutes in order to force the reaction to completion. Rhenium-186 emits both a beta particle and a gamma ray. The beta particle has a maximum energy of 1.07 MeV and the gamma ray is emitted with an energy of 137 keV and 9% abundance. The physical half-life of ^{186}Re is 90 hours. The mechanism of localization for ^{186}Re-HEDP should be the same as its ^{99m}Tc counterpart; in other words, the phosphate portions of the molecule are chemabsorbed into the hydroxyapetite crystal structure of the bone matrix. Since this process is reversible, a portion of the ^{186}Re-HEDP will be constantly released and excreted into the urine.

The FDA has yet to approve ^{186}Re-HEDP, which is still in Phase III evaluation. Mallinckrodt Medical in St. Louis, MO is the manufacturer of the drug. Several studies have been conducted over the last few years involving the use of ^{186}Re-HEDP.[29-34] Most of the published information involving the use of ^{186}Re-HEDP in the United States is prior to 1993.[29-32] Much of the early work using this radiopharmaceutical is summarized by Maxon and associates.[31] According to this article, pain relief of some magnitude was achieved in 77% of the patients treated. Most of the patients suffered from primary cancers of either the prostate or breast, with only 5 patients having other primaries. The dose used in Maxon's studies was about 35 mCi per patient with no variation, even when multiple doses were used. Interestingly, prior to the 1992 article, there are no dosing studies that would indicate what an appropriate dose might be. One of the first attempts at dose ranging originated from the Netherlands and was published by de Klerk[33] in 1994. In this article, 24 patients with prostate cancer were treated with doses of ^{186}Re-HEDP ranging from 35 mCi to 90 mCi. The results seemed to indicate

that the maximum tolerated dose was approximately 80 mCi. Two more recent articles[34,35] from The Netherlands provide follow up information on dosing using ^{186}Re-HEDP. An article by Quirijnen and colleagues[34] provides more information on dose ranges from 35 mCi up to 95 mCi involving a total of 43 patients. In the patient group receiving 35 mCi only 33% were considered to be responders. For a second group of patients who received 50-65 mCi doses, the response rate was significantly better at 78%. When doses of 80-95 mCi were given to a third group, the response rate was 70%. Although the total number of patients studied in the trial was less than 50, the results would appear to indicate that doses in the range of 50-65 mCi, which is similar to those of ^{153}Sm-EDTMP, gave the most pain relief with the fewest side effects. Higher doses are probably not warranted, as the palliation effect is essentially the same as the 50-65 mCi range and the probability of unwanted side effects is increased. A second, more recent, article by de Klerk[35] involving dose escalation states that in bone metastases from prostate cancer, the maximum tolerated dose was again 80 mCi, however patients with metastatic disease from breast cancer could only tolerate doses of 65 mCi. A possible reason for the difference was that patients with breast cancer have a lower marrow production to begin with, due to previous chemotherapy, thus only smaller doses are tolerated. As is the case with the aforementioned agents, ^{186}Re-HEDP causes a transient drop in the marrow production. This usually occurs at about 4-5 weeks post injection with rebound at 8 weeks.

An interesting note on ^{186}Re-HEDP appears in an article by Limouris and Skukla.[36] Stomach uptake of ^{186}Re was observed during imaging. As is seen with ^{99m}Tc labeled bone agents, the uptake was most likely due to perrhenate ion much like the pertechnetate ion uptake observed on bone scans. It was theorized that uptake was due to increased calcium and phosphorus levels and pH levels in the stomach.

Since ^{186}Re-HEDP has not received approval from the FDA, there is no information available on purchasing, calibration or cost of the drug. A new study conducted in Europe involving a large group of patients, has just been completed.[37] The results of this study will determine if Mallinckrodt will pursue an NDA for ^{186}Re-HEDP.

The Alumina-Based Tungsten-188/ Rhenium-188 Generator

Nuclear medicine has a long history of using radioactive generators, mainly for supplying diagnostic radionuclides to end users. In recent years, there has been considerable work from the group at Oak Ridge National Laboratories (ORNL) involving the development of a generator for providing a therapeutic radionuclide, ^{188}Re, which has a variety of applications.[38] One of the possible applications of this radionuclide is the preparation of radiopharmaceuticals for use in palliation of bone pain due to osseous metastases of primary cancers.

The generator produces ^{188}Re in the chemical form of perrhenate which is analogous to the chemical form in which ^{99m}Tc is eluted from a generator. Since we know that ^{99m}Tc in the form of pertechnetate will react with a variety of "cold" reagents to produce various radiopharmaceuticals, similar technology may apply to the production of ^{188}Re drugs. Recently, there have been three articles that describe the preparation,

quality control, and use of various ^{188}Re-labeled agents.[38-40]

The group at ORNL describe the generator and some of its more useful characteristics.[40] The parent radionuclide, ^{188}W, has a relatively long physical half-life of 69 days. This could mean that the generator may be purchased every few months, thus making a considerable impact on the price of the end product. Rhenium-188 has a physical half-life of 16.9 hours. It emits a beta particle that has a maximum beta energy of 2.2 MeV and a gamma ray that has an energy of 155 keV (15% aboundance) which can be imaged. The generator uses an ion exchange column to concentrate and then elute the $^{188}ReO_4$ ion. The elution solvent is normal saline so the product is ready for use in labeling procedures when eluted from the generator.

The article from ORNL as well as others describe the preparation of three different radiopharmaceuticals that can be prepared with ^{188}Re.[38-40] The preparation of ^{188}Re-HEDP is described in two of the articles.[38,39] Each article describes the preparation of the drug, quality control results, and the biodistribution pattern. The paper by Maxon and associates[39] is one of the first reports on the use of ^{188}Re-HEDP in human trials in the United States. In this study, eight men with prostate cancer and metastases to the bone proven with ^{99m}Tc bone scans were given varying doses of ^{188}Re-EHDP. Five of the eight patients received a dose of approximately 35 mCi with the other three receiving doses of approximately 50 mCi. At least one patient who received 50 mCi of the drug experience a "flare" response, with some hematopoietic toxicity being reported in 50% of the patients, and the palliation response rate was determined to be 63%. Overall, it was determined that the ^{188}Re-HEDP results were similar to those obtained by ^{186}Re-HEDP. A second group from Europe have studied the use of pentavalent ^{188}Re-dimercaptosuccinic acid (^{188}Re(V)-DMSA) for the treatment of osseous metastases pain.[40] The uptake of the drug was compared with the uptake of ^{99m}Tc-HDP (oxidronate) on bone scans and it was shown that the ^{188}Re(V)-DMSA only concentrated significantly in the metastatic sites in bone and not in normal bone. The same article also stated that ^{188}Re(V)-DMSA could be prepared by using perrhenate from the aforementioned generator and a DMSA kit that is commercially available in Europe for the preparation of ^{99m}Tc - DMSA. A total of six patients were given ^{188}Re(V)-DMSA and images were obtained at 3 and 24 hours post injection. The results were very encouraging because hematopoietic toxicity may be negligible when compared to other agents, but not enough data is available for accurate dosimetry calculations. One potential problem with this drug is the uptake by the kidneys, as they may receive a relatively large radiation dose. A third drug that has been prepared is ^{188}Re-Octreotide, but it is not used for palliation of bone pain.[38]

Since neither of the described drugs is available for widespread use, there is little information available on the effectiveness, side effects, and cost. The potential for the reduction of costs associated with bone palliation agents may be a factor in the development of this generator.

Tin-117m (Stannic, 4+) Diethylene-triaminepentaacetic Acid (Tin-117m (4+) DTPA)

The development of $^{117m}Sn(+4)$-DTPA was undertaken by Brookhaven National Laboratory (BNL) in an attempt to develop a palliative agent for osseous bone metastases that would have ideal characteristics for therapy with very little, if any, side effects. While no radiopharmaceutical is ideal, this agent has many desirable characteristics. Tin-117m has a physical half-life of 14 days and it decays by both a conversion electron with an energy of 127-129 keV and a gamma ray with an energy of 152 keV (86% abundance). As is the case with other nuclides described previously, ^{117m}Sn is produced in a nuclear reactor. The following equation describes the process:

$$^{117}Sn(n^0,\gamma)^{117m}Sn$$

The tin is produced as an oxide, and then converted to the pure metal by heating prior to irradiation. Once the target is irradiated, it is a rather involved process to produce the $^{117m}Sn(+4)$-DTPA from it.[41] The specific activity can vary greatly depending on the production facility, however it does not seem to affect the uptake of the radiopharmaceutical. The one thing that sets this drug apart from the other therapeutic bone palliation agents, is that conversion electrons are emitted rather than beta particles. Even though they are both electrons, their origin is different. The narrow range of energy exhibited by conversion electrons may make it easier to control the radiation dose given, particularly to the marrow.

In a pilot study,[41] a total of fifteen patients with four different primary cancers that had metastasized to the bone were divided into two groups. Group 1 (7 patients) received $^{117m}Sn(+4)$-DTPA in doses that ranged from 33-84 μCi per kilogram of body weight. Group 2 (8 patients) received doses that ranged from 131-156 μCi /kg of body weight. In Group 1, 4 of 7 patients had partial to complete pain relief and 7 of 8 patients in Group 2 had comparable relief of pain symptoms. Within the two groups, only one patient had a decrease in WBC counts and no significant decrease in platelet counts was observed in any patient.

Since the initial pilot study, several other studies have been completed.[42-46] Krishnamurthy and associates[42] studied the pharmacokinetics of $^{117m}Sn(4+)$-DTPA as well as dose response. Patients received three dosages of 180μCi/kg, 229 μCi/kg, and 285 μCi/kg, respectively. The results indicated that greater than 77% of the injected dose remained in the bone for up to 14 days post injection and pain relief was seen at all three dosing levels. Fourteen patients were studied that had lung, breast, or prostate cancer with metastatic disease to the bone. All three dose ranges gave partial to complete relief of pain in approximately 85% of the patients treated, and no observable marrow toxicity was noted. In a larger study of 40 patients, Srivastava and associates[43] found similar results. In this dose escalation study, patients were given doses ranging from 70-286 μCi/kg body weight. Again, no significant change in either platelet or WBC counts was observed at any dose level and 75% of the patients received some to complete pain relief. In another study by Srivastava and associates[44, 47] patients were studied using five different dose ranges. The results of this report were very similar to the earlier studies with no

correlation between dose ranges and pain relief. The overall pain relief rate was 75%.

Currently ^{117m}Sn(4+)-DTPA is undergoing phase III clinical trials with doses ranging from 10 to 20 mCi. This double blind study, sponsored by Diatide Inc. of Londonderry, NH, compares ^{117m}Sn(4+)-DTPA with Metastron®. Since this drug is not FDA approved, there is no information available about the cost. Based on the production procedures, it most likely will be in the same price range as those agents that are currently approved.

EXTERNAL BEAM RADIATION THERAPY

The use of external beam radiation therapy (EBRT) to treat cancer was first explored in 1944.[47] Since that time EBRT has become the "gold standard" in the use of radiation to treat many types of cancers. According to the literature, as much as 40-50% of all EBRT is used for the palliation of pain.[48,49] Using EBRT for the palliation of pain due to a single site metastatic cancer to the bone has a success rate of 70-90% with 40-50% of the patients reporting complete relief.[48,51] When multiple metastatic sites are present and half-body radiotherapy is used, the palliation success rate is about 70% but only about 20% of the patients reported complete relief. The success rates using hemi-body radiotherapy for multiple metastatic sites are comparable to those of radiopharmaceuticals, but there is no comparison between EBRT and radiopharmaceuticals for single metastatic sites.

There is still a great deal of controversy surrounding the use of EBRT for the palliation of pain due to metastatic disease. This controversy centers on the issue of using several smaller doses of radiation over a 1-2 week period versus using a single larger dose of radiation. The results of both techniques are equivocal according to reports in the literature,[50] while other studies claim one technique is more effective than the other.[51] Controversy arises regarding cost as well as the amount of time it takes to complete therapy, depending on what course is recommended.

The side effects associated with hemi-body radiotherapy can be severe. The most common side effects are nausea and vomiting which can be partially controlled by the use of antiemetics before and during the treatment. Other serious side effects include marrow depression, mucositis, and radiation pneumonitis, with the latter being potentially fatal if not treated immediately.

The costs associated with EBRT can be considerable. It is obvious that a single hemi-body radiotherapy treatment should be less expensive and certainly less time consuming than a course of radiation involving fractionated doses over a 1-2 week period. Since the side effects must usually be treated, this too will add to the cost of the treatment. Overall, the cost of the radiotherapy itself can vary depending on the institution and the type of radiotherapy that is used. Estimated cost can range from $2,000 to $15,000, excluding any costs associated with side effects.

CHEMOTHERAPY AND SURGERY

Chemotherapy and surgery are both useful in controlling bone pain from metastases. Both treatments may diminish pain by decreasing the effects of mechanical pressure. In addition, chemotherapeutic agents may affect the

population of granulocytes, lymphocytes, and monocytes (both within and surrounding a tumor), and may diminish pain by blocking cytokine release from these cells.[51] Because investigators have observed that pain control is not dependent upon the antitumor effects of cytotoxic therapy, it has also been hypothesized that cytotoxic drugs may influence pain by altering both peripheral and central neurotransmitter systems.[51]

Baum and associates list five essential functions of surgery in cancer palliation,[52] among which is control of pain. Surgery is used to relieve obstruction to hollow viscera and debulk a primary tumor, thereby enhancing the effectiveness of radiotherapy and chemotherapy. Surgery may also prevent future pain by preventing the tumor infiltration of nerve roots, especially around the brachial and sacral plexus. The use of surgery is particularly effective where pain is due to mechanical factors or unstable fractures.

ANALGESICS-NSAIDS AND OPIATES

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay in the treatment of bone pain, and the World Health Organization recommends that physicians use NSAIDs as the first step in the analgesic ladder.[53] Bone pain results from the local secretion of prostaglandins, and NSAIDs inhibit prostaglandin synthesis by decreasing the activity of the enzyme, cyclo-oxygenase. Specifically, NSAIDs induce a reduction in the edema, which stretches the periosteum and reduces the prostaglandin-induced pain sensitization.[54] Effectiveness is usually best against pain of low to moderate intensity or as an adjunct for more severe pain.[53] NSAIDs have demonstrated a ceiling effect, defined as a dosage at which a maximum analgesic response is observed, beyond which only further anti-inflammatory effects or increased toxicity occur.[54] Both the effective and toxic dose are unknown in the cancer patient suffering from bone pain. There is a variety of NSAIDs available as over the counter or prescription medications. No conclusive data exists showing which NSAID is more effective, and the choice of a particular drug should be based on the frequency of dosing required, adverse effects, patient history, and cost. The results of controlled clinical trials of NSAIDs in cancer patients with bone pain have not been reported separately from pain not originating in the skeleton; therefore it is difficult to make any specific conclusions on overall effectiveness for this indication.

Adverse effects of NSAIDs are generally related to the inhibition of cyclo-oxygenase.[53] The most common and problematic is their propensity to cause gastrointestinal ulceration. In the stomach, prostaglandins act to increase the production of protective mucosa and decrease acid secretion. [53] Due to the inhibition of prostaglandin synthesis seen with NSAIDs, the patient is at greater risk for the development of an ulcer. The American College of Gastroenterology has developed guidelines to prevent and treat ulcers caused by NSAIDs, and has established categories to determine which patients are at a higher risk. Prophylactic therapy is recommended for patients who are at high-risk for the development of an ulcer.

NSAIDs can also adversely affect platelet and renal function. In normal patients, prostaglandins play a small role

in regulating renal blood flow. However, in patients with chronic renal failure, prostaglandins become more important, and a reduction in glomerular filtration rate may result.

Most, if not all, NSAIDs are highly protein bound (90-99%) and may interact with other highly protein bound drugs, such as warfarin, oral hypoglycemics, and methotrexate. Dosages should be readjusted when combination therapy is necessary.

While most NSAIDs are inexpensive, one needs to consider other costs associated with their use. Medications used for prophylactic ulcer therapy, such as misoprostol, omeprazole, or lansoprazole, can be quite expensive, and need to be considered when choosing the appropriate treatment for bone pain.

If pain persists or increases, the World Health Organization recommends the addition of a weak or strong opioid.[53] This group of analgesics includes all natural and synthetic compounds which interact with the morphine receptors in the CNS and elsewhere.[53] Combination therapy with NSAIDs and an opioid is appropriate since they have different mechanisms of action and act at different levels of the neurological pathways of pain.[53] Opioids, such as morphine, bind to opiate receptors in the CNS, causing inhibition of ascending pain pathways, therefore altering the perception of and response to pain. There is a general CNS depression that results.

Patients will respond to individual opioids differently. Dose-limiting adverse effects may occur with one opioid, while another may provide adequate pain control and no unwanted effects.[53] It is important to understand that switching from one opioid to another may provide a solution for the patient unable to tolerate a specific medication. Adverse effects include sedation, constipation, and nausea and vomiting, and it is these adverse effects that determine the upper limit of opioid dosage. Tolerance to adverse effects usually develops more quickly than tolerance to the analgesic effect, and slow titration of opioids may provide adequate pain control within a few days for most patients.[53]

Problems arise in the presence of significant incident pain and the titration of opioid dosage becomes very difficult.[54] Some patients may require very little baseline opioid doses, however when a movement induces severe pain, adequate drug serum concentrations are not obtained quickly enough.[53] The pain then wears off very quickly, however the drug continues to act for several hours. It is during this interval that possible opioid toxicity could occur. It may be necessary to increase the baseline opioid dosage and counteract dose-limiting sedation with the use of psychostimulant drugs, such as methylphenidate.

It is important to recognize that included in the costs associated with the medications used for the palliation of bone pain, are the costs of treating the unwanted side effects. A pharmaco-economic evaluation needs to take into consideration the dose-limiting adverse effects and include any costs associated with their treatment.

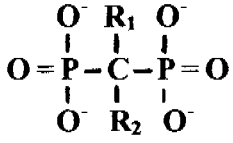
BISPHOSPHONATES

An exciting recent adjunct for treatment of bone metastases is systemic therapy with a bisphosphonate. Table 1 lists the agents in this drug class that have been used for, or show potential use for this indication. Initially developed by the chemical industry to be

used for binding calcium in industrial processes, bisphosphonates have been used as water-softeners, tested as potential additives to toothpaste to prevent the build-up of dental calculus, and evaluated for use in the treatment of coronary atherosclerosis.[55, 56] Since the 1960s, the predominant clinical value of bisphosphonates has been in the treatment of disorders that involve abnormalities of bone mineral metabolism. These include hypercalcemia of malignancy, osteoporosis, Paget's disease, and myeloma. Numerous recent studies have documented their value in treating bone pain, promoting bone healing, and preventing skeletal complications when used in conjunction with anticancer treatments.[55-58]

The structure of bisphosphonates resembles that of pyrophosphates but differs in that it contains a backbone of phosphorous-carbon-phosphorous rather than phosphorous-oxygen-phosphorous (Figure 1). A variety of bisphosphonates have been synthesized by modifying the chemical substituents located on the carbon backbone.[59] This has resulted in second and third-generation agents with 1,000 to 10,000 times greater potency and greater selectivity for bone.

Figure 1.



Bisphosphonates act to inhibit bone resorption through their direct and indirect action on osteoclast activity,[56] although the specific mechanism of decreasing pain is not entirely understood. Bisphosphonates concentrate at sites of active bone remodeling[60] where they bind to hydroxyapetite crystals, the form of calcium phosphate present in bone salts, and inhibit their growth and dissolution. There is also evidence that the drugs are internalized by osteoclasts and interfere with differentiation and specific biochemical processes.[58] Recent studies have shown bisphosphonates to induce osteoclast and tumor cell apoptosis[61, 62] and make it difficult for osteoclasts to recognize exposed unmineralized bone surface.[57] Used as single agents, bisphosphonates have been shown to relieve bone pain associated with breast, prostatic, and other miscellaneous primary cancers. As adjuncts to anticancer therapy, they can prevent skeletal complications, slow down the metastatic process, and improve patient quality of life.[59,60]

Not all bisphosphonates are equally effective in treating morbidity associated with bone metastases. One of the first bisphosphonates available was etidronate, approved for marketing in 1987. While useful in the treatment of Paget's disease, the use of etidronate in treating metatstatic bone pain has been limited by its inhibition of normal bone mineralization.[57] Very few studies have been done to evaluate its use for bone pain, and newer more potent agents have already been marketed. Alendronate is a newcomer to the market, approved by the FDA in 1995. One small, uncontrolled preliminary study was

conducted outside the U.S. and showed oral and parenteral alendronate to have promise in reducing pain in patients with metastatic prostate cancer.[63] However, currently the product is available in the U.S. in oral form only for the indication of osteoporosis.

The bisphosphonates most extensively studied and commonly used in treatment of bone metastases are clodronate and pamidronate. Clodronate is a second-generation bisphosphonate that, unlike etidronate, does not inhibit mineralization of normal bone. Clodronate is available in both oral and injectable forms in Canada and Europe, but not yet in the United States. Several published studies have supported its use in osteolytic bone metastases associated with breast cancer, myeloma and prostatic cancer. Long term treatment with clodronate in patients with metastases from breast and prostate cancer has reduced severity of bone pain, vertebral fractures, and analgesic requirements.[60,63] Diel and colleagues[64] conducted a prospective, randomized, non-placebo-controlled study in 302 patients with primary breast cancer and tumor cells in the bone marrow. Patients received 1600mg of oral clodronate daily for two years in addition to standard therapy or standard therapy without clodronate. There was a significant reduction in the incidence of both osseous and visceral metastases in the clodronate group.[64]

There is no consensus on the optimal dose and schedule of administration for clodronate treatment of bone metastases. Although the oral route is more convenient than intravenous injection, variable patient response necessitates individual treatment. The common oral dose is 1600 mg per day (range 1600 to 3200 mg)[60,63,64] or 300mg per day intravenously for a varied duration. Adami[63] suggests 300mg of Clodronate per day for 5 days followed by additional single IV infusion in responding patients administered at the recurrence of pain. Clodronate should be diluted and administered intravenously over at least 2 hours or by mouth with a full glass of water, at least 1 to 2 hours before or after food.

Pamidronate disodium was approved for marketing in the United States in 1995 for the treatment of normocalcemic patients with myeloma bone disease and in 1996 for treatment of patients with osteolytic lesions of metastatic breast cancer. Pamidronate therapy has also been associated with clinical benefits for skeletal metastases. One study[65] randomized 382 women with metastatic breast cancer and lytic bone lesions into pamidronate or placebo groups. The pamidronate group received 90mg of drug intravenously every 3 to 4 weeks as adjunct to standard chemotherapy. Patients were evaluated every month for 2 years for skeletal complications. At the end of the study period, the pamidronate group required significantly less radiation or surgery to treat bone complications. Despite no demonstrated difference in survival between the two groups, investigators concluded that pamidronate used as a supplement to chemotherapy is more effective than chemotherapy alone in preventing skeletal complications in breast cancer patients. Additional studies support these clinical benefits in patients treated for metastatic prostatic carcinoma[63] and cancer from other primaries.[66]

The recommended dose in patients with osteolytic bone metastases is 90mg administered as a 4-hour infusion monthly. Treatment with high, single-

dose pamidronate (120mg in 1 liter of normal saline) has also been suggested as effective. Purohit and associates[66] conducted a small, open phase II study to assess this treatment regimen on pain and quality of life. The study showed a high frequency of symptomatic response with minor side effects. Retreatment was also successful but only in patients who had demonstrated symptomatic response to the first treatment.

Pamidronate is marketed by Ciba as Aredia® in vials of 30mg and 90mg. It is currently available for intravenous administration only. The dose should be diluted in 500ml of 0.45% or 0.9% NaCl or 5% Dextrose injection and infused over 4 hours.

All bisphosphonates have very poor intestinal absorption when given orally, therefore some investigators have advocated parenteral therapy as the preferential route.[63,66] Patients may not show maximal clinical response to bisphosphonate treatment for up to 4 - 7 days.[67]

Treatment with bisphosphonates is associated with mild adverse reactions. Oral bisphosphonates have very poor oral absorption and medications, foods, and dietary supplements that contain calcium and other minerals may interfere with their absorption. Oral administration is most commonly associated with upper GI symptoms that include nausea, vomiting, diarrhea, and constipation. To minimize these adverse reactions, patients should be advised to take oral medication on an empty stomach 1 to 2 hours prior to a meal and stand or sit upright for at least 30 minutes following the dose. Intravenous administration is also associated with generally mild adverse reactions. No clinically significant side effects due to clodronate therapy were noted in a recent review.[57] Treatment with pamidronate has also been reported to be generally well tolerated, but reports of ocular complications,[68] anemia, hypocalcemia, hyperphosphatemia, transient fever, myalgias, arthralgias, and influenza-like symptoms have been published.[65,66]

Although bisphosphonate treatment with current agents has been shown to reduce skeletal morbidity, there is no evidence that bisphosphonate therapy can alter metastatic disease progression or significantly change patient mortality.[65] Several new agents are currently in investigational trials to evaluate their role in reducing the morbidity associated with bone metastases. These include ibandronate, zoledronate, and olpadronate.[61,69,70]

Bisphosphonate treatment is expensive. The cost will vary as dictated by individual needs, drugs utilized, purchasing source, preparation time, duration of therapy, treatment of adverse reactions, personnel time, and expenses associated with inpatient or outpatient services. The cost of a single-month 90mg pamidronate treatment will exceed $500 when considering average wholesale drug price alone. Although there is little doubt about the value of adjunct bisphosphonate treatment for painful bone metastases, questions remain to be answered concerning its cost-effectiveness.

- Can expensive treatment with bisphosphonates be compensated with savings from reduced treatment of fractures, metastases, and pain?

- What are the savings associated with improved quality of life for patients suffering from painful bone metastases?

Table 1. Bisphosphonates Available for Potential Use in the Palliation of Bone Pain

Generic	Brand (Manufacturer)	Available strengths and routes of administration	Approved Indication	AWP Cost per Dose[+]
Clodronate* disodium	Ostac (Boehringer Mannheim)	30mg/ml injection for slow i.v. infusion; 400 mg capsules	Not approved in the U.S.	Not applicable
Pamidronate disodium	Aredia (Novartis)	30mg, 90mg powder for injection	Neoplasm with hypercalemia; Paget's Disease; Bone metastases	30mg - $231.11 90mg - $652.22
Etidronate disodium	Didronel (Proctor & Gamble; MGI Pharma)	200 & 400mg tablets; 300mg/ampule (6ml amp)	Neoplasm with hypercalcemia; Paget's; Hetertropic ossification	200mg - $2.29 400mg - $4.58 ampule - $67.00
Alendronate sodium	Fosamax (Merck)	5 mg, 10mg, 40mg tablets	Osteoporosis, postmenopausal; Paget's disease	5 & 10mg - $1.90 40mg - $4.80
Tiludronate	Skelid (Sanofi Winthrop)	240mg tablets (equivalent to 200mg tiludronic acid)	Paget's disease	240mg - $7.52
Risedronate	Actonel (Proctor & Gamble)	30mg tablets	Paget's disease	30mg - $12.88

** Not available in the United States; [+] Redbook 1999*

PHARMACOECONOMIC CONSIDERATIONS OF THERAPY

As the clinical alternatives for the treatment of metastatic bone pain expanded during the last decade, concerns about the escalating costs and utilization of health care also increased. Currently, the United States has the most expensive health care system in the world -- one that is growing faster than the rest of the economy.[71] Selection of optimal therapy is very difficult for clinicians when new therapy is expensive and cost containment issues are important. Clinicians, payers, patients, and politicians are all interested in selecting treatment which is most likely to confer the greatest value or worth in terms of clinical, humanistic (quality of life) and economic outcomes. Traditionally, clinical outcomes have provided the basis for the majority of treatment selection decisions. However, there is evidence that clinicians have an increased concern about financial issues. Studies have shown that economic issues

can impact the setting in which care is provided[72] and also influence prescribing preferences over considerations of life extension or drug side effects.[73] Outcomes research seeks to identify, measure, and evaluate the results of health care services. Kozma and associates[74] proposed a multi-dimensional model that provides a comprehensive framework for assessing outcomes by integrating clinical as well as economic and quality of life (humanistic) considerations. The authors termed this model, ECHO, an acronym that represents economic, clinical, and humanistic outcomes.

By definition, "pharmacoeconomics" is a division of outcomes research that involves the economic "description and analysis of the costs of drug therapy to health care systems and society."[75] Pharmacoeconomic research methods provide explicit, systematic ways to compare treatment alternatives that consider costs and outcomes. One such treatment alternative may even include not providing active treatment, because an ill patient will likely continue to consume health care resources even if not receiving treatment. Those costs may even exceed the costs associated with active treatment.[76] Pharmacoeconomics is a tool that helps payers, clinicians, and society decide which treatment is most likely to provide the best patient outcome for the cost.

At present, there are four different pharmacoeconomic research methods in use. These include cost-minimization analysis (CMA), cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), and cost-utility analysis (CUA). The basic similarities and differences between the methods are summarized in Table 2. All four methods measure the costs of healthcare programs or interventions that are being compared in terms of dollars. However, the methods differ in the way in which outcomes or consequences of the programs, or interventions are measured and reported. Which method an investigator decides to use depends upon the information desired. Of the four methods listed above, cost-effectiveness analysis is probably the most frequently used technique currently reported in medical literature.

Table 2. Types of Full Pharmacoeconomic Methods*

	Costs associated with programs or interventions are measured and reported in . . .	Outcomes resulting from programs or interventions are	Results of analysis are reported as . . .
Cost Minimization Analysis	Dollars	Demonstrated by the investigator to be equivalent.	the least costly program or intervention.
Cost Benefit Analysis	Dollars	Measured and reported in dollars	Benefit to cost ratio, Net benefit, and/or Return on investment
Cost Effectiveness Analysis	Dollars	Measured and reported in a single "natural" unit" (e.g. number of cures, number of symptom-free days)	Cost effectiveness ratio and/or Incremental cost-effectiveness ratio
Cost Utility Analysis	Dollars	Measured and reported in Quality-adjust life years (QALYs) or similar measure that incorporates patients' perspective.	Incremental cost utility ratio

* Adapted from Draugalis, JR, Bootman, JL, Larson, LN, McGhan, WF. *Pharmacoeconomics, Current Concepts.* 1989. The Upjohn Company.

Among the first steps in conducting an economic evaluation is identification of the costs and outcomes associated with a treatment or drug regimen. Economic issues regarding the treatment of bone pain are complex, making identification of costs difficult. Portenoy[1] has reported that economic evaluation has been limited by the lack of systematic outcomes research and agreement as to what constitutes optimal treatment for cancer pain. Portenoy has identified and attempted to justify some of the issues and costs associated with therapies for cancer pain. Costs are associated with primary therapy (i.e., surgery, chemotherapy, radiotherapy), analgesic and adjuvant drug use (NSAIDs, opiates, antidepressants, radiopharmaceuticals, bisphosphonates, etc.), drug administration costs (oral, intravenous, intraspinal, subcutaneous routes), treatment of side effects, site of care (hospital, outpatient, home), nursing care, and physician fees. The not-so-obvious costs include indirect and intangible expenses such as reimbursement biases, loss of work,

suffering, home and childcare, and most importantly, loss of quality of life.

Very few published studies compare treatment options for palliation of bone pain either by cost or by cost and outcomes. Therapy that minimizes skeletal morbidity and maximizes patient quality of life is assumed to be cost effective, however, high financial costs associated with new therapy often act as disincentives to their widespread use.[77] Thorough pharmacoeconomic analyses are needed to provide clinicians with more complete and comparative information concerning costs and benefits of treatment alternatives.

Three published studies have evaluated cost and outcome issues related to the use of radiotherapy treatment for metastatic bone pain. McEwan and associates[2,3] conducted a small (n = 14) retrospective cost analysis to estimate the impact of Metastron (strontium-89 chloride) on the management costs of advanced prostate cancer patients. The results support evidence that Metastron use has a positive cost to benefit contribution to the management costs of these patients. Direct costs (including analgesic costs) and tertiary inpatient requirements were reduced. They also noted significant improvement in patient well-being which was not costed. Schmeler and Bastin[78] evaluated the outcomes of hospice-eligible prostatic cancer patients treated with intravenous strontium-89 (^{89}Sr). Their purpose was to determine what patient criteria should be used to justify the risks and costs of ^{89}Sr treatment in contrast to traditional opiate, NSAIDs, and external beam therapy. Patients were categorized and evaluated by Karnosfsky Performance Status Scale (KPS), pain response, toxicity, and actuarial survival. The authors concluded that only patients with a pre-treatment KPS score of 60 or greater should be considered for ^{89}Sr treatment and these patients should have adequate long-term survival to justify the risks and costs. A pilot cost-minimization analysis was conducted by Marklis and associates to identify and compare the costs of brief-course palliative radiotherapy to published costs of narcotic analgesic therapy in treating painful metastases.[79] Patients included in the study had metastases from a variety of cancer types and KPS scores of 70 or greater. The results suggest that the cost of brief-course, palliative radiotherapy, when used as an integral component of a treatment regimen, can be justified in circumstances where it reduces intensive narcotic use.

There are also very few studies that evaluate the cost to benefit use of adjuvant treatment with bisphosphonates. Clodronate therapy is suggested to have significant potential to lower the cost associated with managing metastatic disease of breast cancer. The conclusion is based on a retrospective analysis of direct hospital-based costs. The data also inferred, but did not quantify, the intangible cost benefit resulting from improved patient quality of life resulting from fewer fractures and decreased pain and immobility.[80] In a randomized study, oral pamidronate therapy was reported to improve selected aspects of patient quality of life by significantly decreasing bone pain and mobility impairment in patients with advanced breast cancer.[81] The economic value of these benefits was not measured.

It has been estimated that several factors, including an aging population and increasing cancer incidence, will increase the need for palliative care for cancer patients in the future.[82] When

coupling the high expense of new therapy with growing limitations on health care spending, evaluation of the financial impact of all therapies will be necessary to justify their widespread use. It will also become increasingly important for health care professionals to thoughtfully and systematically integrate economic and humanistic factors into their clinical decision-making.

CONCLUSION

Bone metastasis and associated skeletal pain are frequent complications in patients with neoplastic disease, and their treatment is highly variable. This lesson has reviewed the range of available treatments for the palliation of pain. Since pain contributes to patients' poor quality of life during the end stages of their illness, it is important for clinicians to prescribe adequate treatment for its palliation. Despite the availability and array of therapies, the management of pain often remains inadequate for many patients.[83] Poor pain management of metastatic cancer has been associated with patient gender, race, and treatment setting.

As this lesson illustrates, costs associated with each therapy are highly variable and dependent upon clinical response of the patient and the institution or site of patient care. It is this variability, in conjunction with few published outcome studies concerning optimal pain palliation, that make useful comparison of therapies a difficult task for the clinician.

The difficulty in identifying and measuring appropriate costs of each treatment is also a barrier to conducting pharmacoeconomic studies. These studies must not only consider the direct cost of the treatments, but also indirect costs and intangibles such as loss of quality of life and suffering. Therapies that appear to be expensive due to a high direct cost may actually be less expensive when the savings from indirect costs and intangibles are considered. Consider, for example, the use of radiopharmaceutical therapy vs EBRT or half-body radiotherapy. Radiopharmaceuticals require a one-time injection, which can last from 3-12 months with rare side effects that require medical attention while EBRT or half-body radiotherapy may require multiple treatments daily for 1-2 weeks and often have side effects that require medical attention. Further trials comparing bisphosphonate treatment as adjunct to other options may support the cost-effectiveness of bisphosphonate use.

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QUESTIONS

1. Which of the following radiopharmaceuticals is **not** FDA approved for the palliation of pain due to osseous metastatic disease?
   a. $^{117m}Sn(+4)$-DTPA
   b. $^{89}SrCl_2$
   c. ^{153}Sm-EDTMP
   d. 32P-Sodium Phosphate

2. Which of the following radionuclides may be useful in the palliation of pain due to osseous metastatic disease and is generator produced?
   a. ^{186}Re
   b. ^{188}Re
   c. ^{153}Sm
   d. ^{117m}Sn

3. Highly metabolic metastatic bone tumors will respond better to which of the following FDA approved radiopharmaceuticals?
   a. $^{89}SrCl_2$
   b. ^{186}Re-HEDP
   c. $^{117m}Sn(4+)$-DTPA
   d. ^{153}Sm-EDTMP

4. Complete relief of pain symptoms in patients with multiple metastatic bone sites for both half-body radiotherapy and radiopharmaceuticals occurs in about_____ of all patients treated.
   a. 10%
   b. 50%
   c. 20%
   d. 40%

5. The first radiopharmaceutical to be FDA approved for the palliation of pain due to osseous metastases was?
   a. Metastron®
   b. ^{32}P-Sodium Phosphate
   c. Quadramet®
   d. ^{153}Sm-EDTMP

6. Which of the following FDA radiopharmaceuticals for bone pain palliation is approved for only metastasis from either breast or prostate cancer?
   a. Quadramet®
   b. ^{32}P-Sodium Phosphate
   c. Metastron®
   d. ^{186}RE-HEDP

7. Of the FDA approved palliation radiopharmaceuticals which can be imaged using a gamma camera?
   a. Metastron®
   b. Quadramet®

c. 32P-Sodium Phosphate
d. Both b and c.

8. The recommended dose for 153Sm-EDTMP is?
a. 1.0 mCi/Kg body weight
b. 0.5 mCi/Kg body weight
c. 1.5 mCi/Kg body weight
d. 2.0 mCi/Kg body weight

9. Generally, the most serious side effects occur with the use of____?
a. Metastron®
b. Quadramet®
c. 32P-Sodium Phosphate
d. Half-body radiotherapy

10. A potential agent for use in palliation of bone pain that appears to only take up in metastatic bone sites and not normal bone tissue is?
a. ^{186}Re-HEDP
b. ^{188}Re-HEDP
c. ^{188}Re-DMSA
d. ^{188}Re-Octeotide

11. Which of the following radionuclides emits a conversion electron?
a. ^{117m}Sn
b. ^{153}Sm
c. ^{186}Re
d. ^{89}Sr

12. Which type of primary cancer with metastases to the bone appears to respond best to radiopharmaceutical drugs?
a. Prostate
b. Breast
c. Lung
d. Colon

13. The approximate beta maximum given off by ^{89}Sr is?
a. 1.7 MeV
b. .27 MeV
c. 1.4 MeV
d. .80 MeV

14. Which of the following factors should be considered by both the clinician and the patient when deciding on an optimal therapy?
a. Economic
b. Humanistic
c. Clinical
d. All of the above

15. Chemotherapy has been hypothesized to palliate pain associated with advanced cancer by all of the following mechanisms EXCEPT by:
a. Decreasing mechanical pressure by decreasing tumor size.
b. Binding to receptors in the CNS causing inhibition of ascending pain pathways.
c. Decreasing cytokine production by lymphocytes and granulocytes.
d. Altering peripheral and central neurotransmitter systems.

16. In addition to pain palliation, bisphophonates are commonly used for which of the following disorders?
a. Hypercalcemia of malignancy
b. Osteoporosis
c. Paget's Disease
d. All of the above.

17. Potency and selectivity of bisphosphonates are altered by:
a. Modifying the chemical groups on phosphorous.
b. Substituting the carbon with a heavy metal ion.
c. Modifying the chemical groups located on the carbon backbone.
d. None of the above.

18. Bisphosphonates are thought to act by which of the following mechanisms?
a. Inhibit bone resorption by action on osteoclast activity.
b. Interfere with osteoclast differentiation.
c. Induce osteoclast apoptosis.
d. All of the above.

19. Which of the following of the bisphosphonates is associated with inhibition of normal bone mineralization?

a. Alendronate
b. Etidronate
c. Pamidronate
d. Zoledronate

20. The World Health Organization recommends that practitioners initiate which treatment as the first step of the analgesic ladder?
a. Opiates
b. Corticosteroids
c. Bisphosphonates
d. NSAIDs

21. Combination therapy with NSAIDs and opiates is appropriate because:
a. Each class of drugs works by a different mechanism of action.

b. Each class work at different neurological pathways of pain.
c. Both class of drugs are very inexpensive.
d. a and b only

22. All of the following side effects may occur with the use of opiates EXCEPT:
a. Sedation
b. Constipation
c. Thrombocytopenia
d. Vomiting

23. To minimize the gastrointestinal side effects associated with bisphosphonate use, the patient should be directed to:
a. Take the dose with a full glass of milk.
b. Take the dose with a full glass of water 1-2 hours prior to a meal and remain upright for 30 minutes following the dose.
c. Take the dose with the morning meal.
d. None of the above.

24. The recommended dosage of pamidronate for skeletal complications associated with metastatic bone cancer is:
a. 60mg by mouth daily.
b. 90mg intravenously once a month.
c. 120mg intravenously once a week.
d. 120 mg by mouth once a week

25. Which of the following state-ments are true concerning economic evaluations of the treatment of meta-static bone pain?
a. Pharmacoeconomic analyses provide explicit, systematic evaluations of costs and outcomes of treatment alternatives.
b. Many economics studies have been performed comparing costs and outcomes of current therapy for pain palliation.
c. Pharmacoeconomics can be a useful tool to enable clinicians to integrate economic and humanistic outcomes in their clinical decision-making.
d. a and c