Editorial Reflections
Bisphosphonates For Palliation in Cancer - are we responding?

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Dr. Paul Walker
Palliative Care Unit, Edmonton

Bisphosphonates are analogues of inorganic pyrophosphate. Their use is well established for treatment of osteoporosis and Paget's disease. In the oncology setting, clodronate and pamidronate are the drugs of this class that are most frequently used and studied. The mechanism of action of bisphosphonates is inhibition of osteoclast mediated bone resorption caused by cancer. These drugs have been administered both orally and parenterally, however, the oral bioavailability is extremely poor in the order of less than 5%. Over the last 10 years, this field of research has been growing rapidly and more recently well performed randomized controlled trials (RCTs) have been performed. At present RCTs support the use of bisphosphonates to treat hypercalcemia of malignancy and these drugs are now the agents of choice for this condition. Several RCTs have explored the use of bisphosphonates as an adjunct to assist in controlling bone pain [1-4]. These studies have shown significant benefit in reducing bone pain with minimal side effects in patients with different cancers. Prevention of complications due to osteolysis such as pathological fracture, need for palliative radiotherapy, surgery to treat pathological fractures, and spinal cord compression, have been investigated in breast cancer [5-10] and in multiple myeloma [11-14]. In these studies, complications due to osteolysis were significantly reduced as was bone pain. Three studies [15-17] have confirmed benefit of bisphosphonates for treatment of steroid induced osteoporosis. A recent systamatic review [18] and various expert opinions support the use of bisphosphonates as standard therapy in cancer [19,20].

In spite of this level I evidence from multiple RCTs, in our group's clinical practice it is rare that we see bisphosphonates used other than in the setting of hypercalcemia of malignancy. This leads us to speculate that these drugs may be under-utilized for treatment of bone pain, prevention of complications due to osteolysis, and prevention of steroid-induced osteoporosis. It is apparent that the use of bisphosphonates has increased with the publication of the previously mentioned trials, however it is troubling that many patients are still denied the proven palliative benefits.

As with any new finding it takes time for changes in practice to occur (until recently [14,21] a survival benefit had not been shown, which has now prompted more excitement among the oncology community). However, with the large amount of evidence accumulated it is time to go forward with guidelines for the use of these agents in order to promote palliation. To this end it would be desirable that the groups responsible for cancer care convene to determine consensus guidelines. Standard chemotherapy agents have been utilized with less evidence than we now have for a beneficial effect of bisphosphonates.

Costs remain a considerable concern as these agents are expensive. It is significant praise for the effectiveness of these drugs that others have suggested that cost reductions could occur through

decreases in hospitalization and need for radiotherapy and surgery. However, a cost saving benefit should not be required for implementation as there are few interventions in medicine that actually save money.

Oral administation of these agents has been effective in many studies [4,7,10-12,15-17]. However, due to the extremely poor oral bioavailability of these agents, parenteral administration is often utilized, especially in treating hypercalcemia of malignancy and acute bone pain. The inconvenience of IV administration represents a further obstacle to providing these benefits to our patients. For some groups monthly intravenous infusions of pamidronate have become the standard, however our group has explored the use of subcutaneous administration of clodronate [22,23], which can be conveniently administered in the home via hypodermoclysis and may offer cost savings.

In summary, an evidence based medicine approach supports the use of bisphosphonates based on level I evidence. The responsibility remains with treating physicians to change our practices and overcome the financial and logistic obstacles to bring these benefits to the cancer sufferer.

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