ROLE OF PAMIDRONATE DISODIUM (AREDIA) IN REDUCING SKELETAL RELATED EVENTS IN PATIENTS WITH METASTATIC BONE DISEASE: A PILOT STUDY

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SUMMARY

We present our data of 14 patients (11 male and 3 female) with metastatic bone disease who were treated with Pamidronate disodium (Aredia, Novartis) for the prevention of pathological fractures and for the relief of bone pain due to skeletal metastases at a dose of 60 mg, intravenously, every 28 days. 06 patients had multiple myeloma, 04 patients had advanced carcinoma of the prostate, 02 patients had advanced cancer of the breast while 02 patients had metastases of unknown origin. Pamidronate was administered in a dose of 60 mg as an intravenous infusion, over 2-3 hours every 21 days. Patients have been followed up for over 6 months. 10/14 (70%) patients had a substantial relief of bone pain (25-50% reduction) at this dose within 20 days. Pain reduction was accompanied by improved mobility, performance and quality of life. These patients had a radiological stabilization of bone disease and no new lesions were detected radiologically. None of the patients had a pathological fracture during treatment and follow-up. Pamidronate was well tolerated and side-effects were minimal (03 patients had flu like symptoms and 02 had transient fever). In conclusion, Pamidronate (Aredia) significantly reduces skeletal morbidity, delays the development of bone metastases and fractures, provides significant relief of bone pain, reduces the use of analgesics and is well tolerated with a good safety profile. Patients with skeletal involvement due to cancer may therefore benefit from the use of Pamidronate administered either alone or in combination with cancer chemotherapy.

INTRODUCTION

Bone metastases are one of the commonest manifestations of certain types of advanced cancers. More than 70% of patients with malignant melanoma, cancer of breast, lung, prostate and kidney will eventually develop bone metastases while 15% of these patients will have pathological fractures due to osseous metastases. Multiple myeloma, a hematologic malignancy of plasma cells, is characterized by osteolytic bone destruction resulting in skeletal related morbidity. Metastases from melanomas, lung, breast and kidney tumors are osteolytic primarily. Metastases from prostate cancer are predominantly osteoblastic but they also have an underlying lytic component which contributes to the symptoms of bone pain. This bone destruction occurring due to bone metastases results in excruciating pain, pathological fractures, spinal cord compression (skeletal morbidity) as well as tumor induced hypercalcemia resulting in increased morbidity and mortality in these patients. These complications result from increased osteoclastic resorption of the bone.
TABLE I
TYPES OF MALIGNANCIES IN PATIENTS TREATED WITH PAMIDRONATE (AREDIA)

<table>
<thead>
<tr>
<th>Type of Malignancy</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple myeloma patients</td>
<td>06</td>
</tr>
<tr>
<td>Carcinoma of the prostate patients</td>
<td>04</td>
</tr>
<tr>
<td>Carcinoma of the breast patients</td>
<td>02</td>
</tr>
<tr>
<td>Metastases of unknown origin patients</td>
<td>02</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>14</td>
</tr>
</tbody>
</table>

by cancer/myeloma cells. These destructive effects are mediated by local production of a variety of osteoclast stimulating factors including growth factors such as parathyroid hormone (PTH), parathyroid hormone related peptide (PTH-rP), 1-25 (OH)2 vitamin D3, TGF b, TNF etc. by tumor cells, which in turn stimulate the action of osteoclasts.4

Bisphosphonates are a novel class of drugs developed over the last two decades for therapeutic as well as diagnostic use. These are analogues of pyrophosphates, a naturally occurring substrate, known to inhibit the dissolution of calcium hydroxyapatite crystals in vitro as well as ectopic calcification.5 Bisphosphonates inhibit bone resorption both in vivo as well as in experimental systems.5 This had led to its investigation of their use in malignant as well as non-malignant osteolytic conditions.5,6 These compounds act by inhibiting osteoclastic activity by the following mechanisms.5,7

i  inhibition of osteoclast maturation
ii prevention of osteoclast migration towards the bone
iii binding firmly to preformed bone surface making the bone less accessible to osteoclasts.

Among the various bisphosphonates investigated for the inhibition of bone resorption, bone pain and tumor induced hypercalcemia, Pamidronate Disodium (Aredia, Novartis) has been found to be the most potent so far.5,8 Pamidronate is a second generation bisphosphonate that inhibits bone resorption at doses that does not affect bone mineralization9 and also normalizes serum calcium levels within a few days.10

In various studies, bisphosphonates have been shown to inhibit the incidence of skeletal complications including bone pain, pathological fractures and spinal cord compression and have also resulted in healing of osteolytic lesions in patients with bone metastases due to a variety of cancers.11,16 The dose used in most of these studies was 90 mg, intravenously. This dose repeated every three to four weeks is considered to be the optimum dose although 60 mg every 3-4 weeks has also shown almost similar results in the preliminary dose finding studies.17

We performed a pilot study at Medical A Ward, Lady Reading Hospital, Peshawar, to study the effect of Pamidronate (Aredia, Novartis) at a dose of 60 mg every 4 weeks on skeletal related complications and severe bone pains due to skeletal metastases not responding to analgesics. 14 patients with a variety of advance cancers suffering from severe bone pains unresponsive to chemotherapy and analgesics were included in the study to study the effect of Aredia on bone pain and skeletal complications at a dose of 60 mg every 4 weeks considering the high cost of the drug and limited financial resources of our patients.

MATERIAL AND METHODS

Eligibility criteria included: age >18 years, life expectancy >3 months, negative pregnancy test, radiologically visible bone metastases/lytic lesions with severe bone pain not responding to routine analgesics, no previous history of bisphosphonate administration, no radiation therapy within the past
15 days, s. creatinine <3.5 mg/dl, s. bilirubin <2.5 mg/dl, TLC >3500/cumm, Platelets >100000/cumm and no significant ECG changes/cardiac problems.

Pain evaluation was performed as follows (according to linear analogue scale):
- Complete relief: no pain experienced at all, no analgesia required.
- Partial relief: 50% reduction in baseline pain/analgesic use.
- Minimal relief: 25% reduction in baseline pain/analgesic use.
- No relief: Pain/analgesic use equal to or greater than baseline.

Pamidronate (Aredia, Novartis) was administered in a dose of 60 mg as slow intravenous infusion over 2-3 hours every four weeks.

RESULTS

A total of 14 patients (11 male and 03 female) were with advanced metastatic bone disease/myeloma and severe bone pains were included in the study. Age of these patients ranged from 45-72 years. Types of malignancies is shown in Table-1. Pamidronate was administered in dose described above. Patients have been followed up for more than six months.

10/14 (70%) patients had a substantial relief from bone pain (25-50% reduction) usually occurring within 20 days after the initiation of treatment. Pain reduction was also accompanied by improved mobility, performance as well as improved quality of life. These patients also had a radiological stabilization of their lytic lesions and no new lytic lesions were detected radiologically in the six months follow-up period. None of the patients had a pathological fracture during the six months study period.

Pamidronate was well tolerated by all patients and side-effects were minimal. These side-effects included flu-like symp-

toms (3 patients) and transient fever (2 patients).

DISCUSSION

The commonest symptom of bone metastases reported by patients is bone pain. This is mostly localized to a particular area but may be generalized in case of multiple myeloma or widespread metastases. This pain results due to local destruction of the bone by tumor cells which activates osteoclasts. Tumor cells produce various growth factors and prostaglandins which in turn activate osteoclasts. This increased osteoclastic activity results in bone destruction resulting in bone pain. The rationale for the use of bisphosphonates in prostate cancer is not clear cut since the lesions in this disease are blastic. However, there is bone resorption as well as formation going on at the same time, with resorption mostly preceding bone formation. These patients also have a marked increase in s. alkaline phosphatase and other markers of bone destruction.17

The aim of our study was test the efficacy of Pamidronate in our population with a wide variety of metastatic carcinomas, including prostate cancer, in a dose of 60 mg given every three weeks. Our results show a good response of Pamidronate in limiting skeletal related morbidity including bone pain. More than two thirds of patients had a substantial reduction in bone pain and no new lesions or fractures were noted in the study period. Half the patients with prostate cancer also responded indicating that Pamidronate has activity in metastatic prostate cancer as well. These results are in conformity with other studies described above11,16 and indicates that this drug has significant activity even when given in a dose of 60 mg every three weeks.

In conclusion, Pamidronate (Aredia) significantly reduces the rate of skeletal morbidity, delays the development of bone metastases, gives significant relief from
bone pain, reduces the use of analgesics and is well tolerated with a good safety profile. Patients with skeletal involvement due to cancer may therefore benefit from the use of Pamidronate administered either alone or in combination with chemotherapy. Trials are ongoing to study the efficacy of Pamidronate given adjuvantly with chemotherapy in early stage cancers in order to prevent skeletal metastases from occurring at all.

REFERENCES


