Clinical Analysis of Bisphosphonates Treatment on Bone Metastases and Hypercalcemia of Malignancy in Advanced Solid Tumor

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ABSTRACT

Objective: To evaluate the efficacy and toleration of bisphosphonates therapy in patients with bone metastases and hypercalcemia of malignancy in advanced solid tumor. Methods: Patients with histologically or cytologically confirmed cancer and hypercalcemia with bone metastases were designed to open treatment with either 4mg zoledronic acid or 90mg pamidronate. The primary efficacy parameters were pain scores (NRS), Corrected serum calcium (CSC) and CSC effective rate. The vital signs, biochemical and hematological parameters were determined. Results: Twenty patients were enrolled in this study, twelve patients in zoledronic acid group and eight in pamidronate group. Zoledronic acid and pamidronate significantly palliated pain. Pain scores were significantly lower at end-point after zoledronic acid or pamidronate infusion (5.92 vs 3.25, \(P<0.01\); 6.13 vs 4.38, \(P<0.01\), respectively). The mean CSC level decreased significantly after zoledronic acid or pamidronate infusion from 12.86 to 10.28mg/dl and 13.19 to 10.36mg/dl respectively. The CSC effective rate was about 90% at 14 days after infusion in two groups. There was no statistical significance for all primary efficacy parameters in zoledronic acid group compared with pamidronate group. An adverse reaction was mild fever after pamidronate infusion and then completely reversible. Conclusion: Zoledronic acid and pamidronate disodium were well tolerated and effective for bone metastases and hypercalcemia of malignancy in advanced solid tumor.

Key words: Carcinoma; Bone metastases; Hypercalcemia of malignancy; Bisphosphonates

Hypercalcemia of malignancy (HCM) is the most serious complication of malignancy in the late stage. It occurs in 10% to 15% of patients with advanced cancer, but the frequency is now decreasing because of an earlier and prolonged use of bisphosphonates in cancer patients with bone metastases \(^{[1]}\). But the incidence of HCM is only 0.92‰ in China \(^{[2]}\). The early symptoms of HCM are mild and difficult to distinguish from symptoms of the underlying disease or the side effects of cancer therapy. If left untreated, it can progress rapidly and may become life-threatening. Patients who develop HCM generally have a short life expectancy. We have recently assessed the evidence for the role of intravenous bisphosphonates in carcinoma patients with bone metastases and HCM.

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PATIENTS AND METHODS

Patients

Patients with histological or cytological confirmation of cancer, proved bone metastases by ECT and X ray or CT or MRI examinations, and hypercalcemia, defined as an albumin-corrected serum calcium (CSC) \(\geq 12.0\) mg/dl, were eligible. The pain scales (Numerical rating scale, NRS) were \(\geq 5\). The CSC was calculated by the following formula: CSC \((\text{mg/dl}) = \text{patient's measured serum calcium (mg/dl)} + 0.8\times[\text{mid-range serum albumin of laboratory standard (g/dl)} - \text{patient's measured albumin (g/dl)}]^{[3]}\). Patients who had a history of allergic reaction to bisphosphonates or who had been treated with bisphosphonates for HCM within 3 months of study entry were excluded, as were patients who exhibited serum creatinine>4.5mg/dl or who were treated with calcitonin within 72 h of study entry. Patients who were treated with newly initiated antineoplastic
cytotoxic chemotherapy or hormonal therapy 6 days before or 10 days after the initial administration of this study drug, or with any investigational drugs within 1 month of study entry were also excluded. Additional exclusion criteria were for patients who were severely dehydrated, could not tolerate intravenous hydration, or suffered from hyperparathyroidism, adrenal insufficiency, vitamin D intoxication, milk alkali syndrome, sarcoidosis or other granulomatous disease, or multiple endocrine neoplasia syndromes.

Treatment

Patients were randomly treated with a single dose of 4mg zoledronic acid with 100ml of 0.9% sodium chloride via a 15 min intravenous infusion or 90mg pamidronate with 500ml of 0.9% sodium chloride via intravenous infusion over 4h after intravenous hydration. Then patients were followed-up for 14 days.

Assessment of Safety and Efficacy

The primary efficacy parameters were assessed by the CSC level and NRS, which were measured on days 7 and 14 after infusion. The CSC effective level is less than 12mg/dl. The CSC effective rate is the cases of the patients’ CSC<12mg/dl/total cases in each group. The clinical findings, adverse reactions, vital signs, biochemical and hematological parameters were determined.

 Statistical Methods

We used Chi-squared test to evaluate the CSC effective rate in two groups. F test was used to analyze measurement data of the CSC and NRS( x±s). P≤0.05 was considered significant.

RESULTS

Patient Characteristics

Twenty patients were enrolled in the study, 12(male 5, female 7) including seven lung cancer, four breast cancer and one prostate cancer patients were treated with zoledronic acid, 8(male 5, female 3) including five lung cancer and three breast cancer patients were treated with pamidronate. All patients’ symptoms were difficult to distinguish from symptoms of primary cancer or side effects of cancer therapy, such as weak, suppression, anorexia, nausea, abdominal pain, polyuria, confusion and coma. Table 1 lists the characteristics of the treated patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age(y)</th>
<th>High(m)</th>
<th>Weight(Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zol</td>
<td>12</td>
<td>58.8±13.2</td>
<td>1.65±0.08</td>
<td>63.0±8.8</td>
</tr>
<tr>
<td>Pam</td>
<td>8</td>
<td>63.1±8.4</td>
<td>1.67±0.08</td>
<td>67.3±5.3</td>
</tr>
</tbody>
</table>

NRS and CSC Changes

Both zoledronic acid and pamidronate resulted in decreases in pain scores and CSC. The reduction of CSC and NRS were similar in the two groups (Table 2).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>NRS Baseline</th>
<th>NRS D7</th>
<th>NRS D14</th>
<th>CS Baseline</th>
<th>CS D7</th>
<th>CS D14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zol</td>
<td>12</td>
<td>5.92±0.79</td>
<td>4.14±1.47</td>
<td>3.25±1.54</td>
<td>12.86±0.59</td>
<td>10.63±1.03</td>
<td>10.28±1.28</td>
</tr>
<tr>
<td>Pam</td>
<td>8</td>
<td>6.13±0.99</td>
<td>4.63±1.60</td>
<td>4.38±1.69</td>
<td>13.19±0.75</td>
<td>11.14±0.95</td>
<td>10.36±1.33</td>
</tr>
</tbody>
</table>

P values vs baseline: *P<0.01; P values vs D7 after of treatment: **P<0.01

The CSC Effective Rate

The CSC effective rate on Day 7 and 14 after treatment in Zoledronic acid group were 75%(9/12) and 91.7%(11/12) respectively, 75%(6/8) and 87.5%(7/8) in pamidronate group respectively. No significant difference was showed between the zoledronic acid group and the pamidronate group.