Combining Systemic Bisphosphonates with Palliative External Beam Radiotherapy or Bone-Targeted Radionuclide Therapy: Interactions and Effectiveness

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Introduction

Bisphosphonates, external beam radiotherapy and bone-seeking radiopharmaceuticals (BSRs) have an established role for the management of metastatic bone disease. Radiotherapy achieves significant pain relief and a decrease in local skeletal complication rates [1]. The exact mechanism by which pain relief is achieved is unknown. It has been suggested that a high level of tumour and inflammatory cell kill and the subsequent decrease in osteoclastic activity play a role [2–4]. BSRs bring about a similar effect in areas of increased uptake by local radiation emission. These mechanisms may be an important link for the possible synergistic activity with bisphosphonates.

In recent years, bisphosphonate use has increased dramatically in patients with bone metastases, becoming an integral part of their overall management [2]. Their application has been shown to reduce metastatic bone pain and the risk of skeletal-related events [5,6]. Moreover, bisphosphonates preserve or even improve the quality of life of treated patients [6]. Bisphosphonates have a selective effect on osteoclasts, reducing their activity and viability [2].

Interactions between Radiotherapy and Bisphosphonates: Synergistic Activity, Spatial Co-operation and Normal Tissue Tolerance

The vicious cycle of osteolytic bone metastases [7] involves the release of osteoclastic mediators from tumour cells, which results in increased bone resorption, the release of growth factors, and tumour cell proliferation that further promotes bone lysis [2,8]. The common action of radiotherapy and bisphosphonates on osteoclasts implies a potential synergistic activity in regions of bone metastases, enabling osteoblasts to achieve enhanced re-ossification and promote bone remodelling [3,9,10]. In animal models of tumour-induced osteolysis, the combined use of radiotherapy and bisphosphonates has been shown to result in re-ossification and improved bone micro-architecture, bone volume and biomechanical strength [11,12]. The enhanced bone formation may be responsible for the significant pain reduction and favourable clinical response reported in studies evaluating the combination of radiotherapy and bisphosphonates, as it was recently shown that metastatic bone pain has a strong negative and statistically significant correlation with bone density [13].

In addition to synergistic activity, the combination of radiotherapy and bisphosphonates brings about spatial co-operation, with radiotherapy controlling local bone destruction and bisphosphonates hindering metastatic progression in skeletal regions outside the treatment field [2,3]. Furthermore, having independent limiting toxicities, side-effects are not additive.

Results of Clinical Studies Investigating the Effectiveness of Combined External Beam Radiotherapy and Bisphosphonates

Eight clinical studies that evaluate the concomitant application of radiotherapy and bisphosphonates have been identified [9,10,14–19], as shown in Table 1. These are all relatively small single institution phase II studies; there is to date no randomised phase III study comparing radiotherapy alone with a radiotherapy/bisphosphonate combination. One study [19] has attempted historical comparison with a control radiotherapy-alone group and suggested improved rates of re-ossification, but made no claims for pain control.
Concurrent Application of Radionuclides and Bisphosphonates

BSRs comprising beta-emitting radionuclides such as samarium-153 or strontium-89 are useful in controlling pain from widespread metastatic bone disease [20,21]. Following intravenous injection, a selective delivery of ionising radiation to targeted areas of amplified osteoblastic activity occurs, and multiple (symptomatic and asymptomatic) metastases are targeted simultaneously.

BSRs are approved for the palliative treatment of advanced prostate cancer, but have not gained a wide acceptance in the oncological community. A renewed interest has been seen [22], with recent studies using concomitant use of BSRs and chemotherapy showing that the combination is both feasible and effective [23-25].

One study evaluated pain refractory to conventional treatments [26], treating with either six infusions of zoledronate (4 mg) every 3 weeks, followed by a single dose of 150 MBq strontium-89 (group A, n = 25), or strontium alone (group B, n = 13), or zoledronate alone for 8 months (group C, n = 11). A statistically significant pain reduction was noted for all groups, but for group A patients the pain response was more pronounced (P < 0.001); 68% of group A patients had a pain response ≥ 4 points, as compared with 15 and 9% for groups B and C, respectively.

In a study including 41 women with breast cancer and disseminated bone metastases, patients were treated with either rhenium (Re-186 HEDP) and pamidronate or Re-186 HEDP alone [27]. The investigators reported that the bisphosphonate application did not interfere with the radionuclide uptake or effect; pain reduction measured by the visual analogue scale was similar and statistically significant for both groups. In a further study, 48 breast cancer patients with metastatic bone disease received either rhenium (Re-188 HEDP) (group A), pamidronate alone (group B), or Re-188 HEDP plus pamidronate (group C) [28]. Pain relief for groups A–C was 73.3%, 80 and 100%, respectively, and the corresponding rates for objective bone metastases response was 40, 33.3 and 67.7%. The investigators concluded that the combined treatment resulted in a significantly better therapeutic effect (P < 0.05).

Conclusions and Future Perspectives

Neither radiotherapy nor bisphosphonates are completely effective in managing bone metastases when used as monotherapies [3]. This conclusion is derived from the fact that 30-40% of breast cancer patients and 15-20% of those with multiple myeloma receiving bisphosphonates will undergo radiotherapy due to persisting pain or impending fracture [3], despite the fact that bisphosphonate use has been shown to reduce the overall need for radiotherapy.

The combination of radiotherapy and bisphosphonates achieves a significant response in terms of pain relief and improvement of quality of life and performance status that may be superior to that achieved when either therapy is applied alone, but this has yet to be rigorously tested. There is a strong theoretical basis for synergistic activity between the two modalities to achieve enhanced reossification in metastatic lesions [2], supported by animal studies showing that combined treatment achieves improved biomechanical strength, stability and bone microarchitecture [11,12]. The combination of radionuclide therapy (BSRs) with bisphosphonates has also been shown to be effective, and may be particularly useful in patients with pain from multiple skeletal metastases refractory to conventional treatments.

The promising results published so far reveal a new therapeutic perspective for managing bone metastases, which must now be explored further in large randomised studies. This will be addressed by the International Consensus Conference Workshop.

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Table 1 – Results of clinical trials using combined radiotherapy and bisphosphonates

<table>
<thead>
<tr>
<th>Reference</th>
<th>Assessment time (months)</th>
<th>Pain reduction (points)</th>
<th>Complete pain response</th>
<th>PS improvement (points)</th>
<th>QoL improvement (points)</th>
<th>Bone density changes</th>
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<tbody>
<tr>
<td>[14]</td>
<td>52</td>
<td>2</td>
<td>VAS: 7</td>
<td>—</td>
<td>—</td>
<td>31% complete recalcification</td>
</tr>
<tr>
<td>[15]</td>
<td>18</td>
<td>6</td>
<td>BPS: 6.3</td>
<td>—</td>
<td>ECOG: 1.9</td>
<td>MVGLH: 11.6% increase</td>
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<tr>
<td>[16]</td>
<td>42</td>
<td>6</td>
<td>BPS: 6.7</td>
<td>—</td>
<td>ECOG: 2.7</td>
<td>MVGLH: 17 units increase</td>
</tr>
<tr>
<td>[17]</td>
<td>33</td>
<td>6</td>
<td>BPS: 5.8</td>
<td>—</td>
<td>ECOG: 2.4</td>
<td>MVGLH: 9.5% increase</td>
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<tr>
<td>[9]</td>
<td>45</td>
<td>6</td>
<td>VAS: 5.7</td>
<td>71%</td>
<td>KPS: 23.8</td>
<td>46% increase in HU</td>
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<tr>
<td>[10]</td>
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<td>6</td>
<td>VAS: 6.9</td>
<td>53%</td>
<td>KPS: 23.8</td>
<td>234.1% increase in HU</td>
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<tr>
<td>[18]</td>
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<td>10</td>
<td>VAS: 8.5</td>
<td>72.2%</td>
<td>KPS: 24.3</td>
<td>203.2% increase in HU</td>
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<td>[19]</td>
<td>23</td>
<td>6–9</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Radiotherapy + bisphosphonates: improved re-ossification</td>
</tr>
</tbody>
</table>

HU, Hounsfield units; MVGLH, mean value grey level histogram; PS, performance status; KPS, Karnofsky performance status; ECOG, Eastern Cooperative Oncology Group; VAS, visual analogue scale; BPS, bone pain score; QoL, quality of life.

*Lytic group. |Physical functioning scale.
COMBINING BISPHOSPHONATES WITH PALLIATIVE RADIOTHERAPY

References


