Clinical guideline for the administration of Bisphosphonates and other drugs affecting bone metabolism in Haematology and Oncology patients

1. Aim/Purpose of this Guideline
   1.1. To provide education to nursing staff about the use of drugs that affect bone metabolism.
   1.2. To provide nursing staff administering bisphosphonate infusions safe guidance on which to do so.

2. The Guidance
   2.1. Bones

   2.1.1. Bones are made up from two layers. The outer portion of bone is called the bone cortex, while the centre of the bone is called cancellous bone. The bone marrow is contained within the spaces of the cancellous bone.

   2.1.2. Although bone is made up of minerals and is hard, it is still a living tissue containing blood vessels, nerves and cells, including two very important cell types which play a key role in the normal activity of bones – these are:

   - Osteoblasts (cells which form new bone)
   - Osteoclasts (cells which break down old bone)

   2.1.3. The cycle of bone breakdown and formation keeps the bone in a continual state of renewal. This ongoing process is known as bone remodelling and maintains the thickness, strength and health of bones throughout the body.

   2.1.4. Normally, the rate of bone formation and the rate of bone breakdown are equal, so that the bone mass remains the same.

   2.1.5. Cancer cells can cause bones to breakdown by producing signals and substances known as cytokines and growth factors that activate bone breakdown but which inhibit new bone formation.

   2.1.6. Specifically, these signals and cytokines increase the activity of the osteoclasts and at the same time reduce the activity of osteoblasts.
2.2. What do Bisphosphonates Do?

2.2.1. Bisphosphonates are small inorganic molecules that bind to calcium and as a result are taken up into bone.

2.2.2. They inhibit the activity of the osteoclasts and interrupt the increased bone breakdown.

2.2.3. Bisphosphonates therefore have several potential beneficial effects including:

- Preventing / slowing down further bone breakdown
- Reducing bone pain and the need for pain-killers
- Preventing and correcting hypercalcaemia
- Reducing the need for radiotherapy
- Reducing the likelihood of pathological fractures due to bone disease
- Improving quality of life, particularly by decreasing pain and maintaining mobility
- Improving the chances of healing and recovery of strength of bone

2.3. Potential side-effects of Intravenous Bisphosphonates:

2.3.1. Bisphosphonates are generally well tolerated. Any side-effects are usually mild and the most common ones are nausea, fever, flu-like symptoms, impaired kidney function and bone pain.

2.3.2. Fever and flu-like symptoms can occur shortly after the intravenous infusion. They are typically mild and last for only two to three hours. The effects are usually successfully treated with paracetamol.

2.3.3. Vein irritation may occur at the site of the infusion. Again, it is usually mild and patients recover within one to two days.

2.3.4. General bone aches and pains sometimes occur and are mostly linked to the onset of fever and / or flu-like symptoms. They can persist for a day or two after each infusion and can be managed with pain-killers such as paracetamol.

2.3.5. Nausea that is mild and short lasting is quite common with oral bisphosphonates.

2.3.6. Impaired kidney function is probably the most important potential side-effect. All bisphosphonates can potentially harm kidney function.

2.3.7. Bisphosphonates should be used with caution in patients who have impaired kidney function.

2.3.8. Osteonecrosis of the Jaw (ONJ):

2.3.8.1. ONJ is defined as the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks of identification by a healthcare professional.
2.3.8.2 To help prevent ONJ it is recommended that prior to commencing bisphosphonates patients should have a dental examination and appropriate preventive dentistry should be considered prior to treatment with bisphosphonates, particularly in patients with poor dental status. Any dental treatment needed should be carried out prior to the start of therapy.

2.3.8.3 While on treatment, these patients should avoid invasive dental procedures if possible. If dental work is required during treatment the dentist should be made aware that the patient is receiving bisphosphonates. There are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

2.3.8.4 If ONJ is suspected patients should be referred to the oral surgeons as dental surgery may exacerbate the condition.

2.3.8.5 During the course of bisphosphonate treatment, all patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling.

2.3.8.6 Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

2.4. Administration of Intravenous Bisphosphonates

2.4.1. Pamidronate:

2.4.1.1. Indication:
- Osteolytic lesions and bone pain in metastases associated with breast cancer or multiple myeloma 90mg every 4 weeks (or three weekly to co-inside with chemotherapy regimens in Breast cancer.)
- Hypercalcaemia of malignancy according to serum calcium concentration 15-60mg in single infusion or in divided doses over 2-4 days, maximum of 90mg per course

2.4.1.2. Infusion:
- Compatible with 5% Glucose or 0.9% sodium Chloride
- Aredia dry power: Reconstitute initially with 10mls of water for injection and further dilute with infusion fluid to a concentration of not more than 60mg in 250mls.
- Disodium Pamidronate dilute with infusion fluid to a concentration of not more than 60mg in 250mls or 90mg in 500mls.
- Do not exceed administration rate of 1mg/minute or 20mg/hr in renal impairment.
- Not to be administered with calcium infusions.

2.4.1.3. RCHT Nurse Administration Guidance for Standard Treatment
• **Haematology patients:**
  - All infusions will be prescribed by the patient’s Consultant, Haematology SPR or Chemotherapy/Haematology Clinical Nurse Specialist who will have reviewed the most recent renal function results available and dose adjusted accordingly.
  - Nursing staff will administer the prescribed dose of pamidronate, observing the most recent renal function results that are available, up to one month old.
  - If the patient has not had a blood test taken that day, the nursing staff will take a blood test in preparation for the patient’s next dose. They will label the blood test with the name of the patient’s haematology consultant, for the consultant to observe.
  - If there is a discrepancy between the patients renal function the consultant will observe this and prescribe the next dose accordingly. It is accepted that that days dose may have already have been administered and therefore be too late for action on the day.
  - If the patient has not had a blood test within one month period, nursing staff will take blood and wait for the results before proceeding with that day’s dose.

• **Oncology**
  - Renal function should be assessed pre each dose by using eGFR.
  - This should be done within 10 days of each treatment.
  - No treatment should occur if eGFR is less than 30/ml/minute/1.73m2 without Consultant approval.

• **Both**
  - The administrating nurses should ensure that the patient is adequately hydrated.
  - Patients should be advised not to drive or operate machinery immediately after treatment as somnolence or dizziness can occur.
  - Serum Calcium should be monitored and corrected as required.

2.4.2. **Zoledronic Acid:**

2.4.2.1. **Indication**
  - Reduction of bone damage in advanced malignancies.
  - Hypercalcaemia of malignancy

2.4.2.2. **Infusion**
  - Compatible with 5% Glucose or 0.9% sodium Chloride
  - Dilute dose with 100mls of infusion fluid and infuse over 15minutes
  - Do not mix or administered with calcium infusions.
2.4.2.3. RCHT Nurse Administration Guidelines for Standard Treatment

- **Haematology**
  - All infusions will be prescribed by the patient’s Consultant, Haematology SPR or Chemotherapy/Haematology Clinical Nurse Specialist who will have reviewed the most recent renal function results available and dose adjusted accordingly.
  - Nursing staff will administer the prescribed dose of Zoledronic Acid observing the most recent renal function results that are available, up to one month old.
  - If the patient has not had a blood test taken that day, the nursing staff will take a blood test in preparation for the patient’s next dose. They will label the blood test with the name of the patient’s haematology consultant, for the consultant to observe.
  - If there is a discrepancy between the patients’ renal function the consultant will observe this and prescribe the next dose accordingly. It is accepted that that days dose may have already have been administered and therefore be too late for action on the day.
  - If the patient has not had a blood test within one month period, nursing staff will take blood and wait for the results before proceeding with that day’s dose.

- **Oncology**
  - Renal function should be assessed pre each dose, by observing baseline creatinine clearance
  - This should be done within 10 days of each treatment.
  - The following dose reduction should occur in renal impairment:

<table>
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<tr>
<th>Baseline creatinine clearance (ml/min)</th>
<th>Dose 3-4 weekly</th>
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<tbody>
<tr>
<td>&gt;60</td>
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<tr>
<td>50-60</td>
<td>3.5*mg</td>
</tr>
<tr>
<td>40-49</td>
<td>3.3*mg</td>
</tr>
<tr>
<td>30-39</td>
<td>3.0*mg</td>
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</table>

*Doses have been calculated assuming target AUC of 0.66 (mg Hr/l) (CLcr+75ml/min). The reduced doses for patients with renal impairment are expected to achieve the same AUC as that seen in patients with creatinine clearance of 75ml/min

*Treatment should be withheld if renal function has deteriorated. In the clinical trials, renal deterioration was defined as follows:*
• For patients with normal baseline serum creatinine (< 1.4 mg/dl or < 124 μmol/l), an increase of 0.5 mg/dl or 44 μmol/l;
• For patients with abnormal baseline creatinine (> 1.4 mg/dl or > 124 μmol/l), an increase of 1.0 mg/dl or 88 μmol/l.

• Both
  o Ensure patient is well hydrated before each dose.
  o Serum Calcium should be monitored and corrected as required.

2.4.3. **RCHT Nurse Administration Guidelines for Acute Treatment**

In the case of Bisphosphonates being required for the treatment of Hypercalcaemia please discuss with relevant medical team and refer to BNF.

2.5. **Alternative drugs affecting Bones Metabolism: Denosumab**

2.5.1. Denosumab is a monoclonal antibody with affinity for nuclear factor- kappa ligand (RANKL). Osteoblasts secret RANKL, RANKL activates osteoclast precursors and subsequent osteolysis which promotes release of bone-derived growth factors. Denosumab binds to RANKL which in solid tumors decreases osteolastic activity leading to decreasing skeletal related events and tumor induced bone destruction

2.5.2. Denosumab is recommended as an option for preventing skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from breast cancer and solid tumors, other than prostate if:

  • Bisphosphonates would otherwise be prescribed and
  • the manufacturer provides Denosumab with the discount agreed in the patient access scheme.

2.5.3. Renal function and calcium level should be monitored

2.5.4. **Dose and administration**

2.5.4.1. 120mg subcutaneous injection once every 4 weeks, into the upper arm, thigh or abdomen.

2.5.4.2. Prior to administration bring to room temperature in original container (allow to stand for 15-30minutes) do not warm by any other method. Solution may contain trace amounts of translucent to white particles, do not use if cloudy, discoloured or contains excessive particles. Avoid vigorous shaking

2.5.4.3. Patient should receive 500mg calcium and 400IU vitamin D throughout treatment.

Clinical guideline for the administration of Bisphosphonates and other drugs affecting bone metabolism in Haematology and Oncology patients V3.0
2.5.4.4. No dose adjustment is required in patients with renal impairment.

2.5.5. Monitoring Parameters

2.5.5.1. Dental checkup should be considered before commencing treatment as there is a risk of osteneocrosis of the jaw, see above.

2.5.5.2. There is a risk of hypocalcaemia if eGFR is less than 30ml/min/1.73m², monitor plasma- calcium concentration levels

2.5.5.3. Osteoporosis, bone mineral density of the hip or spine should be carried out prior to initiation of therapy and at least every 2 years.

2.5.5.4. Annual measurements of height and weight

3. Monitoring compliance and effectiveness

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<td>Chemotherapy MDT and Unit Managers of Headland and Lowen ward</td>
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<td>Tool</td>
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<td>Reporting arrangements</td>
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<td>Required changes to practice will be identified and actioned within 3 months. A lead member of the team will be identified to take each change forward where appropriate. Lessons will be shared with all the relevant stakeholders</td>
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4. Equality and Diversity

4.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the 'Equality, Diversity & Human Rights Policy' or the Equality and Diversity website.

4.2. Equality Impact Assessment
The Initial Equality Impact Assessment Screening Form is at Appendix 3.
Appendix 1. References


- Novartis Pharmaceuticals UK Ltd Summary of Product Characteristics (SmPC) for the Zometa 4 mg/5 ml concentrate for solution for infusion formulation. Accessed via www.medicines.org.uk/EMC on 05/04/2012.

- Denosumab: Drug Information Lexicomp Accessed via www.UpToDate.com on 24/04/2013
### Appendix 2. Governance Information

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<td>June 2016</td>
</tr>
<tr>
<td>Date Valid From:</td>
<td>June 2016</td>
</tr>
<tr>
<td>Directorate / Department responsible (author/owner):</td>
<td>Sarah Caskey, Clinical Matron</td>
</tr>
<tr>
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<td>Guideline for the safe administration of bisphosphonates infusions and other drugs affecting bone metabolism.</td>
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<td>Cancer, chemotherapy, Bisphosphonate, Haematology, Oncology, Denosumab</td>
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<td>Medical Director</td>
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<td>March 2016</td>
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<tr>
<td>Divisional Manager confirming approval processes</td>
<td>Bryson Pottinger, Clinical Director CSCS</td>
</tr>
<tr>
<td>Name and Post Title of additional signatories</td>
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<tr>
<td>Name and Signature of Divisional/Directorate Governance Lead confirming approval by specialty and divisional management meetings</td>
<td>{Original Copy Signed}</td>
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<tr>
<td>Signature of Executive Director giving approval</td>
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Clinical guideline for the administration of Bisphosphonates and other drugs affecting bone metabolism in Haematology and Oncology patients V3.0

Publication Location (refer to Policy on Policies – Approvals and Ratification):

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Document Library Folder/Sub Folder

Clinical / Cancer services

Links to key external standards

None

Related Documents:

References see Appendix 1

Training Need Identified?

No

Version Control Table

<table>
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<th>Summary of Changes</th>
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<td>Bridget Law</td>
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<td>V2.0</td>
<td>Amendments and put into Trust format.</td>
<td>Lisa Nicholls Chemotherapy CNS</td>
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<td>V3.0</td>
<td>• Format updated to current RCHT Clinical Guideline template</td>
<td>Sarah Caskey, Clinical Matron</td>
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This document is to be retained for 10 years from the date of expiry.

This document is only valid on the day of printing

Controlled Document

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### Appendix 3. Initial Equality Impact Assessment Form

<table>
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<tr>
<th>Name of the strategy / policy / proposal / service function to be assessed (hereafter referred to as policy) (Provide brief description):</th>
<th>Clinical guideline for the administration of Bisphosphonates and other drugs affecting bone metabolism in Haematology and Oncology patients</th>
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<tr>
<td>Directorate and service area:</td>
<td>Cancer Services</td>
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<tr>
<td>Name of individual completing assessment:</td>
<td>Sarah Caskey, Clinical Matron</td>
</tr>
<tr>
<td>Telephone:</td>
<td>07767 300479</td>
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1. **Policy Aim***  
   Who is the strategy / policy / proposal / service function aimed at?  
   To provide Clinical Guideline for the administration of Bisphosphonates and other drugs affecting bone metabolism in Haematology and oncology patients.

2. **Policy Objectives***  
   To provide Clinical Guideline for the administration of Bisphosphonates and other drugs affecting bone metabolism in Haematology and oncology patients.

3. **Policy – intended Outcomes***  
   The safe administration of Bisphosphonates and other drugs affecting bone metabolism in Haematology and oncology patients.

4. *How will you measure the outcome?*  
   Through the administration of bisphosphonate using ARIA

5. Who is intended to benefit from the policy?  
   Patients and nursing staff

6a) Is consultation required with the workforce, equality groups, local interest groups etc. around this policy?  
   Yes

   b) If yes, have these *groups been consulted?*  
   Yes

   C). Please list any groups who have been consulted about this procedure.  
   Chemotherapy MDT, all haematology and oncology consultants

### 7. The Impact

Please complete the following table.

<table>
<thead>
<tr>
<th>Are there concerns that the policy could have differential impact on:</th>
<th>Yes</th>
<th>No</th>
<th>Rationale for Assessment / Existing Evidence</th>
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Clinical guideline for the administration of Bisphosphonates and other drugs affecting bone metabolism in Haematology and Oncology patients V3.0
**Clinical guideline for the administration of Bisphosphonates and other drugs affecting bone metabolism in Haematology and Oncology patients**

**V3.0**

**Page 12 of 12**

| Sex (male, female, transgender / gender reassignment) | ✓ |
| Race / Ethnic communities /groups | ✓ |
| Disability - learning disability, physical disability, sensory impairment and mental health problems | ✓ |
| Religion / other beliefs | ✓ |
| Marriage and civil partnership | ✓ |
| Pregnancy and maternity | ✓ |
| Sexual Orientation, Bisexual, Gay, heterosexual, Lesbian | ✓ |

You will need to continue to a full Equality Impact Assessment if the following have been highlighted:
- You have ticked “Yes” in any column above and
- No consultation or evidence of there being consultation- this excludes any policies which have been identified as not requiring consultation. or
- Major service redesign or development

8. Please indicate if a full equality analysis is recommended. [Yes] [No]

9. If you are not recommending a Full Impact assessment please explain why.

No evidence for potential differential impact

| Signature of policy developer / lead manager / director | Date of completion and submission |
| Names and signatures of members carrying out the Screening Assessment | 1. Sarah Caskey |
| | 2. |

Keep one copy and send a copy to the Human Rights, Equality and Inclusion Lead, c/o Royal Cornwall Hospitals NHS Trust, Human Resources Department, Knowledge Spa, Truro, Cornwall, TR1 3HD

A summary of the results will be published on the Trust’s web site.

Signed ____________________

Date ____________________