Hyponatremia/hypercalcemia
Electrolyte disorders in lung cancer

Therapeutinc emergencies in lung cancer
ELCC 2016
15.4.2016
Lung cancer patient pathway

- GP Referral
- Radiology referral
- A & E Referral

- Rapid Access Clinic
- LID

- MDT

- Oncology
  - Chemotherapy
  - Palliation
Impact of metabolic disorders

- GP Referral
- Radiology referral
- A & E Referral
- Rapid Access Clinic
- MDT
- Oncology
- Too UNWELL To ADMIT
- Chemotherapy
- Palliation
Time intervals from first symptom to treatment of cancer:
a cohort study of 2,212 newly diagnosed cancer patients

BMC Health Serv Res. 2011; 11: 284.
Survival in Patients with Hyponatremia and Cancer

Survival (n=3357) according to the lowest serum sodium during hospitalization

Eunatremia (135-147 mEq/L)
Mild hyponatremia (130-135 mEq/L)
Severe hyponatremia (<120 mEq/L)
Moderate hyponatremia (120-129 mEq/L)

Cumulative Survival

Days

0 15 30 45 60 75 90

Log rank P<0.01

Symptoms of hyponatraemia may reduce patient wellbeing

- Headache
- Lethargy
- Poor concentration
- Depressed mood
- Lack of attention
- Impaired memory
- Nausea
- Restlessness
- Gait instability
- Falls
- Muscle cramps
- Tremor

- Confusion
- Disorientation
- Somnolence
- Vomiting
- Hallucinations
- Acute psychosis
- Limb weakness
- Dysarthria

- Seizures
- Hemiplegia
- Severe somnolence
- Respiratory insufficiency
- Coma
- Death

Mild/moderate

Advanced/moderate

Severe

Adapted from Gross P. Ther Adv Endocrinol Metab. 2012;3:61-73
Hospital Length of Stay

Berardi R et al. Support Care Cancer. 2015;
Cost of Hospitalization

Berardi R et al. Support Care Cancer. 2015.
Incidence of HN

• Analysis of 9 clinical trials at 4 hospitals (n=1684)$^1$
  – Serum sodium $< 136$ mEq/L found in **24.6%**

• Retrospective study of patients admitted to M.D. Anderson Cancer center in 2006 (n=3358)$^2$
  – Serum sodium $< 135$ mEq/L found in **47%** of all patients
    • 36% mild (130-134 mEq/L)
    • 10% moderate (120-129 mEq/L)
    • 1% severe (<120 mEq/L)

SCLC and autoantibodies

**Panel A:**
- SCLC + Anti-Hu positive (16% of SCLC)
- Anti-Hu positive + No SCLC (~15% of Anti-Hu positive)
- Neuroblastoma; prostate cancer; rhabdosarcoma; no SCLC found
- PEM/SN + Anti-Hu positive + No SCLC (~15% of PEM/SN)
- Neuroblastoma; no SCLC found

**Panel B:**
- SCLC + Anti-VGCC positive (5% of SCLC)
- LEMS + Anti-VGCC negative + No SCLC (50% of LEMS)
- NSCLC; prostate carcinoma; breast; no SCLC found; other autoantibodies
- LEMS + Anti-VGCC + no SCLC (~7% of LEMS); no SCLC found
- LEMS + Anti-VGCC + SCLC (43% of LEMS)

**Panel C:**
- SCLC + Anti-SOX positive (~27% of SCLC)
- LEMS + Anti-SOX positive + No SCLC (2% of LEMS); No SCLC found
- LEMS + Anti-SOX negative + No SCLC (50% of LEMS); No SCLC found; other autoantibodies
- LEMS + Anti-SOX positive + SCLC (32% of LEMS)
- LEMS + Anti-SOX negative + SCLC (~16% of LEMS)

**Panel D:**
- SCLC + Anti-Rc positive (~10% of SCLC)
- Anti-Rc positive + No SCLC
- Melanoma; Gynecologic cancer; Colon cancer; NSCLC; no SCLC found (20% of Anti-Recoverin)
- CAR + Anti-Rc positive + No SCLC
- Melanoma; Gynecologic cancer; Colon cancer; NSCLC; no SCLC found (55% of CAR)
- CAR + Anti-Rc positive + SCLC (45% of CAR)
Medications That May Cause Hyponatremia

- Amiodarone
- Amitriptyline
- Bromocriptine
- Carbamazepine
- Cisplatin
- Chloropropamide
- Cyclophosphamide
- Haloperidol
- Ifosfamide
- Imatinib
- Interferon-alfa
- Interferon-gamma

- Melphalan
- Methotrexate
- Nivolumab
- Pembrnzulimab
- Opioids
- Oxcarbamazepine
- Sodium valproate
- SSRIls
- Thiothixine
- Vinblastine
- Vincristine

Survival in Corrected Hyponatremia

Two-year and median survival for patients with SCLC by hyponatremia status

<table>
<thead>
<tr>
<th>Status</th>
<th>2-year OS (%)</th>
<th>Median OS (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hyponatremia</td>
<td>30.8 ± 1.3</td>
<td>1.01 ± 0.04</td>
</tr>
<tr>
<td>Hyponatremia corrected to ≥138 mEq/L</td>
<td>29.0 ± 8.0</td>
<td>1.11 ± 0.12</td>
</tr>
<tr>
<td>Refractory (&lt;138 mEq/L)</td>
<td>13.1 ± 6.9</td>
<td>0.43 ± 0.16</td>
</tr>
</tbody>
</table>

CLINICAL MANIFESTATIONS

- **Mild (Na⁺ > 125)**
  - Asymptomatic
  - Malaise
  - Headache
  - Anorexia
  - Nausea
  - Irritability

- **Moderate (Na⁺ 120 – 125)**
  - Vomiting
  - Unstable
  - Confusion

- **Severe (Na⁺ < 120)**
  - Coma
  - Convulsions
  - DEATH

Appropriate Initial Therapy?

- Restrict all fluid intake, not just water.
- Aim for intake that is 500 mL/day below the 24-hour urine volume.
- Do not restrict sodium or protein intake unless indicated.

Predictors of the likely failure of fluid restriction:
- High urine osmolality (>500 mOsm/kg H$_2$O)
- Urine Na$^+$ plus K$^+$ concentrations > serum Na$^+$
- 24-hr urine volume <1500 mL/d
- Increase in serum Na$^+$ <2 mEq/L/day in 24-48 hrs
Rationale For Management of Hyponatremia in Patients With Cancer

• Clinical relevance
  – Hyponatremia is associated with a diminished response to treatment
  – Correction and stabilization of sodium levels is necessary to undertake chemotherapy

• Significance of symptoms

• Improved outcomes
  – Hospitalized cancer patients with hyponatremia have higher mortality rates and longer lengths of stay

• Quality of life

Hyponatremia treatment algorithm

Euvolemic hyponatremia (SIADH)

LEVEL 3 – SEVERE SYMPTOMS
vomiting, seizures, obtundation, respiratory distress, coma

hypertonic NaCl, followed ± vaptan

LEVEL 2 – MODERATE SYMPTOMS
nausea, confusion, disorientation, altered mental status

Vaptan or hypertonic NaCl, administration

vaptan under select circumstances:
- inability to tolerate fluid restriction or failure of fluid restriction
- unstable gait and/or high fracture risk
- very low sodium level (<125 mEq/L) with increased risk of developing symptomatic hyponatremia
- need to correct serum [Na+] to safer levels for surgery or procedures, or for ICU/hospital discharge
- prevention of worsened hyponatremia with increased fluid administration
- therapeutic trial for symptom relief

LEVEL 1 – NO OR MINIMAL SYMPTOMS
: headache, irritability, inability to concentrate, altered mood, depression

## Response To Therapy

Initial therapy in patients from US and EU hyponatremia registry

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline Na⁺ mEq/L</th>
<th>Median Rate of Change mEq/L/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>507</td>
<td>127.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Fluid restriction (≤1000 mL)</td>
<td>399</td>
<td>123.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Fluid restriction (&gt;1000 mL)</td>
<td>529</td>
<td>126.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Normal saline</td>
<td>428</td>
<td>123.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Hypertonic saline</td>
<td>72</td>
<td>118.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>131</td>
<td>124.0</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Hypertonic Saline Correction

- Choose desired correction rate of plasma [Na⁺] (e.g., 1.0 mEq/L/h)
- Obtain or estimate patient’s weight (e.g., 70 kg)
- Multiply weight X desired correction rate and infuse as ml/h of 3% NaCl (e.g., 70 kg X 1.0 mEq/L/h = 70 ml/h infusion)

**OR:**
- 100-200 ml bolus infusion (5-10 min) of 3% NaCl, repeat every 30 min until goal reached
- FOR ALL SALINE CORRECTIONS:
  - Follow serum [Na⁺] and urine output every 2-4 hrs during the active correction

Appropriate Use of Vasopressin Receptor Antagonists

- Patients with SIADH
- Patients who are symptomatic (serum sodium <130 mEq/L)
- Not indicated for patients with depletional hyponatremia or cerebral salt wasting
- Exclude hypovolemic hyponatremia
- Hepatic failure is a relative contraindication

Hypercalcemia of malignancy

- PTHrP mediated hypercalcemia
- Osteolytic metastases mediated hypercalcemia
- Hypercalcemia secondary to overproduction of 1,25 vitamin D
- PTH mediated hypercalcemia (parathyroid carcinoma and ectopic production)
Prevalence of hypercalcemia of malignancy among cancer patients in the UK
United Kingdom Clinical Practice Research Datalink

• Hypercalcemic patients (CSC ≥ 10.8 mg/dL) were classified into 4 CSC levels

• Among 37,442 cancer patients in 2003-2012 the prevalence of grade 1 HCM increased from 0.13% to 0.45% and the prevalence of HCM overall (grade 1 or higher) increased from 0.20% to 0.67%

• Prevalence estimates varied across cancer type and were highest for lung cancer, multiple myeloma and patients with stage IV cancer.

• Our findings suggest that HCM in general is not a common condition

# Hypercalcemia in lung cancer

<table>
<thead>
<tr>
<th>Potential factors</th>
<th>Number of cases</th>
<th>Median survival time (days)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43</td>
<td>90</td>
<td>0.026</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>225</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>17</td>
<td>246</td>
<td>0.022</td>
</tr>
<tr>
<td>( \geq 60 )</td>
<td>47</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Pathological subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>22</td>
<td>80</td>
<td>0.32</td>
</tr>
<tr>
<td>Nonadenocarcinoma</td>
<td>30</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>12</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Peak value of albumin-corrected calcium (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.9</td>
<td>46</td>
<td>188</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( \geq 2.9 )</td>
<td>18</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatases (U/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 120 )</td>
<td>38</td>
<td>182</td>
<td>0.043</td>
</tr>
<tr>
<td>&lt;120</td>
<td>26</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 80 )</td>
<td>26</td>
<td>186</td>
<td>0.106</td>
</tr>
<tr>
<td>&lt;80</td>
<td>38</td>
<td>45</td>
<td></td>
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<tr>
<td>Bone metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29</td>
<td>55</td>
<td>0.122</td>
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<tr>
<td>No</td>
<td>35</td>
<td>182</td>
<td></td>
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<tr>
<td>Liver metastasis</td>
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</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>47</td>
<td>0.106</td>
</tr>
<tr>
<td>No</td>
<td>43</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>Brain metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15</td>
<td>66</td>
<td>0.041</td>
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<tr>
<td>No</td>
<td>49</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>Adrenal metastasis</td>
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<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>90</td>
<td>0.799</td>
</tr>
<tr>
<td>No</td>
<td>55</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>Number of distant metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td>562</td>
<td>0.003</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>( \geq 3 )</td>
<td>27</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>
Diagnostic workflow

**Hypercalcemia**
- **Mild and asymptomatic**
  - Repeat calcium. Consider checking ionized calcium
  - Hypercalcemia confirmed
  - Check PTH and PTHrp
  - If non-diagnostic consider checking vitamin D levels, review medication lists. Consider hypercalcemia due to bone metastases in an appropriate clinical scenario
- **Moderate to severe**
  - Treat while awaiting the results of the work up
  - Hypercalcemia excluded. Stop work up
Pharmacologic therapeutic options for the management of hypercalcemia

<table>
<thead>
<tr>
<th>Agent</th>
<th>Typical dose</th>
<th>Mechanism of action</th>
<th>Modification based on underlying renal and liver disease</th>
<th>Onset of action</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal saline</td>
<td>200-300 milliners/hour, lower rate in patients with underlying cardiac and kidney disease</td>
<td>Volume repletion, increased renal calcium clearance</td>
<td>Consider lower rate in patients with underlying renal disease</td>
<td>Within hours of administration</td>
<td>Volume overload, non-anion gap metabolic acidosis</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>4-8 international units/kg subcutaneously or intramuscularly</td>
<td>Inhibition of osteoclast activity and increase in renal calcium clearance</td>
<td>No dosage adjustment is needed</td>
<td>Within 4 h of administration. Tachyphylaxis develops after 48 h</td>
<td>Nausea, rhinitis, hypersensitivity reactions</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Zoledronic acid 4 mg administered IV over 15 min; pamidronate 60-90 mg administered IV over 2-24 h; ibandronate 2-6 mg administered IV over 1-2 h</td>
<td>Inhibition of osteoclast activity, osteoclast apoptosis and improved osteoblast survival</td>
<td>Zoledronic acid: Do not use in patients with creatinine &gt;4.5 mg/dl (consider increasing the infusion duration in patients with kidney disease); no need for hepatic adjustment Pamidronate and ibandronate: Do not use if glomerular filtration rate is &lt;30; no need for hepatic adjustment</td>
<td>Within 2-4 days after administration. Do not repeat administration earlier than 1 week after the previous IV infusion</td>
<td>Flu-like symptoms, bone aches, nephrotic syndrome, acute kidney injury, osteonecrosis of the jaw</td>
</tr>
<tr>
<td>Denosumab</td>
<td>120 mg subcutaneously</td>
<td>Impairs osteoclast activity</td>
<td>No need for renal and hepatic adjustment. Consider half dose for patients with renal disease to decrease the risk of hypocalcemia</td>
<td>Within 2-4 days after administration. Do not repeat administration earlier than 1 week after the previous dosing</td>
<td>Bone pain, nausea, diarrhea, shortness of breath, osteonecrosis of the jaw and possibly increase in the risk of infections after long-term use</td>
</tr>
</tbody>
</table>
Denosumab mode of action

a monoclonal antibody against the receptor activator of nuclear factor κB ligand, and the calcimimetic cinacalcet

Denosumab rescue therapy

Conclusions

• Hyponatremia is a common electrolyte disorder in patients with cancer and associated with a more negative prognosis.

• The incidence of hyponatremia varies widely among different cancer types with a relatively high prevalence in SCLC.

• Hyponatremia is often caused by SIADH in cancer patients; ectopic secretion of ADH may be important.

• Hypercalcemia in lung cancer is a potential life threatening complication and is not as frequent as HN.

• Persistent hypercalcemia requires parathyroid hormone pathway workup and immediate initiation of therapeutic options.