Brief update on….

Dr Mary Miller

01.03.2019

Topics

- Seizures – Dr Kiely
- Olanzapine
- Gastroparesis
- Denosumab
- Calciphylaxis

Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults

With thanks to Dr Anna Sutherland
ST5 Palliative Medicine Thames Valley
Cochrane UK Fellow Feb 2016- Nov 2017

Systematic review

- Kris 2011:"one of the largest misconceptions in the field of oncology today is that the problem of chemotherapy-induced nausea and vomiting (CINV) has been solved" whilst "CINV is the most significant side effect of chemotherapy from the patient's perspective"
- Cohen 2007: 47% of patients experience CINV
- Teunissen 2007: A systematic review of symptom prevalence in patients with terminal cancer reported pooled prevalence of 31% (95% CI 27-35) for nausea and 20% (95% CI17-22) for vomiting

Olanzapine

- Second generation atypical anti-psychotic
- Most often administered orally
- Tablet (2.5 mg to 20 mg), velotab, oral solution, or orally-disintegrating "wafer“
- Off licence if used as an anti-emetic (EMA)

Adverse effects?

- Weight gain
- Sedation
- Lose of control of diabetes mellitus
- Blood dyscrasias
- Extra-pyramidal side effects and dyskinesias
- Prolongation of the QTc interval

- Excess deaths and strokes reported in dementia patients – class effect

Receptors involved

- Serotonin 5-HT2a, 5-HT2c, 5-HT3, 5-HT6 receptors
- Dopamine D1, D2, D3, D4 brain receptors
- ∝1 adrenergic receptors
- Acetylcholine (ACh) muscarinic receptors
- H1 histamine receptors

Receptors and Anti-emetics?

Anti-emetic	Dopamine D_2 antagonist	Histamine H_1 antagonist	Acetylcholine antagonist	5-HT_2 antagonist
Metoclopramide*	++	–	–	–
Domperidone†	++	–	–	–
Cyclizine	–	++	++	–
Hyoscine	–	–	+++	–
Haloperidol	+++	–	–	–
Levomepromazine	++	+++	++	+++

– none or insignificant; + slight; ++ moderate; +++ marked. * Metoclopramide in higher doses >= 100 mg, demonstrates 5-HT_3-receptor antagonism. † Domperidone does not cross the blood brain barrier so the risk of extrapyramidal adverse effects (such as tremors, slurred speech, and dystonia) is negligible.

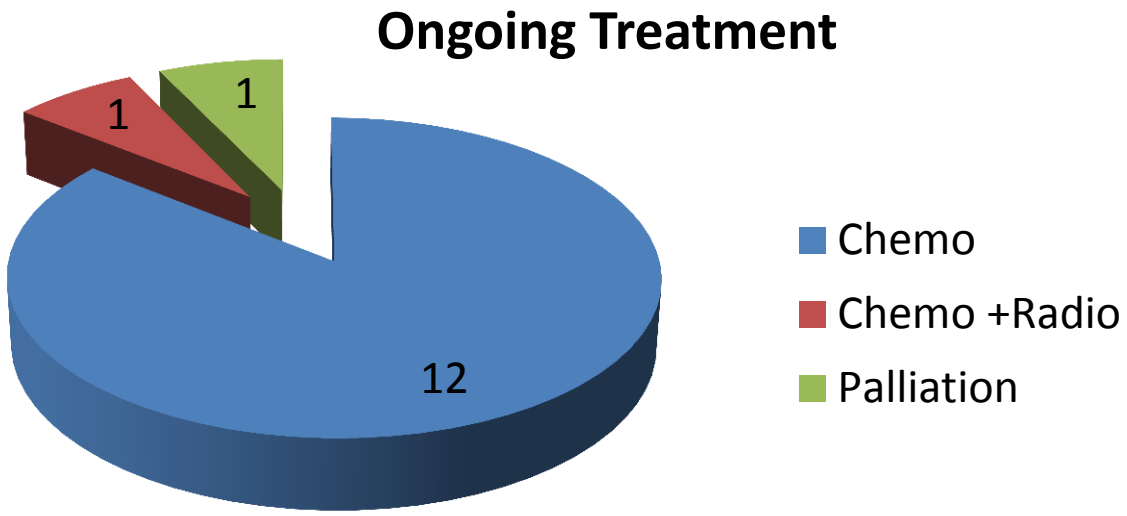
Information from: [Twycross, 2014]

Characteristics of Included Studies

- 14 RCTs (1917 participants)
- Oral administration only
- 24 different cancers
- Male and female
- Ages 18 to 81 years
- None pharma funded

- 8 studies awaiting classification
- 13 studies ongoing

Were Participants Having Active Treatment?



Comparisons

- Main:
- Olanzapine versus placebo/usual care

- Others:
- Olanzapine versus prokinetics
- Olanzapine versus 5HT3 antagonists
- Olanzapine versus NK1 antagonists
- Olanzapine versus dexamethasone

Olanzapine + Usual Care versus Usual Care +/- Placebo

- 9 studies (1000 participants)
- Lu 2013, Mizukami 2014, Mukhopadhyay 2016, Navari 2010a, Navari 2016a, Nikbakhsh 2016, Wang 2015, Zhang 2017, Zhao 2014

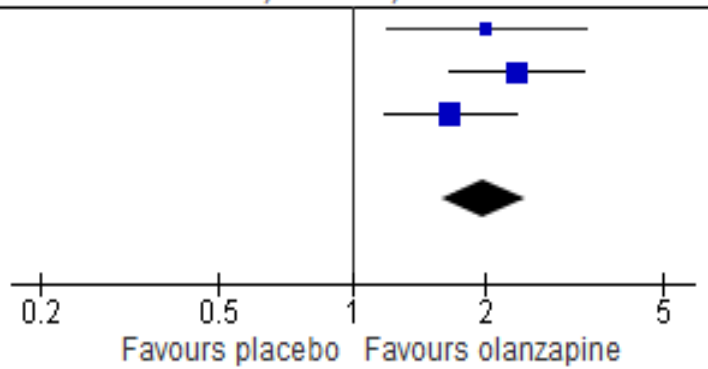
Absence of Both Nausea and Vomiting

Olanzapine + Usual Care versus Usual Care +/- Placebo

Study or Subgroup	Olanzapine Events	Olanzapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Lu 2013	22	30	11	30	18.2%	2.00 [1.19, 3.36]
Mukhopadhyay 2016	47	50	20	50	40.6%	2.35 [1.66, 3.32]
Navari 2016a	66	202	39	199	41.2%	1.67 [1.18, 2.35]
Total (95% CI)		**282**		**279**	**100.0%**	**1.98 [1.59, 2.47]**
Total events	135		70			

Heterogeneity: Tau² = 0.00; Chi² = 1.99, df = 2 (P = 0.37); I² = 0%

Test for overall effect: Z = 6.07 (P < 0.00001)



Olanzapine **probably doubles the likelihood not being nauseous or vomiting during chemotherapy from 25% to 50%** (RR 1.98, 95% CI 1.59 to 2.47; 561 participants; 3 studies; solid tumours; HEC or MEC therapy; ***moderate-quality evidence***) when added to standard therapy.

Number Needed to Treat for additional benefit (NNTB) was 5 (95% CI 3.3-6.6).

Adverse Events

- Uncertain if olanzapine increases the risk of serious adverse events

  NNH (Number Needed to Harm) 152

  (absolute risk difference 0.7% more, 95% CI 0.2 to 5.2; 7 studies, 889 participants, low-quality evidence)

- May increase other adverse events

  NNH (Number Needed to Harm) 19

  (RR 1.71, 95% CI 0.99 to 2.96; 332 participants; 4 studies; low-quality evidence)

- Probably increases somnolence and fatigue

  (RR 2.33, 95% CI 1.30 to 4.18; anticipated absolute risk 8.2% more, 95% CI 1.9 to 18.8; 464 participants; 5 studies; moderate-quality evidence)

- No increase in Withdrawals due to All Causes

  (RR 0.99, 95% CI 0.57 to 1.73; participants = 943; studies = 8; I^2 = 0%)

- No reported deaths

5mg versus 10mg per 24 Hours

- Subgroup of Olanzapine vs Placebo/usual care

  Lu 2013 (2.5mg BD, 60 participants)
  Mukhopadhyay 2016 (10mg OD, 100 participants)
  Navari 2016a (10mg OD, 401 participants)

- Unclear if 5mg as effective as an antiemetic as 10mg
- 5mg may lower the risk of somnolence and fatigue than 10mg

Olanzapine versus NK1 Antagonists

- 1 study
- Shumway 2015 (20 participants)
- No significant difference was observed in any reported outcomes

Olanzapine versus a Prokinetic

- 1 study
- Navari 2013 (112 participants)
- Olanzapine may increase freedom from overall nausea (RR 2.95, 95% CI 1.73 to 5.02) and overall vomiting (RR 3.03, 95% CI 1.78 to 5.14) compared to metoclopramide

Olanzapine versus 5-HT3 Antagonists

- 1 study
- Nakagaki 2017 (62 participants)
- Participants with CINV during bone marrow transplant following chemotherapy +/- total body irradiation

- Olanzapine may increase the likelihood of 50% or greater reduction in nausea or vomiting at 48 hours (RR 1.82, 95% CI 1.11 to 2.97) and 24 hours (RR 1.36, 95% CI 0.80 to 2.34)

Olanzapine versus Dexamethasone

- 1 study
- Liu/Tan 2015 (229 participants)

- Olanzapine may reduce:

overall nausea (RR 1.73, 95% CI 1.37 to 2.18)

overall vomiting (RR 1.27, 95% CI 1.10 to 1.48)

delayed nausea (RR 1.66, 95% CI 1.33 to 2.08)

delayed vomiting (RR 1.25, 95% CI 1.07 to 1.45)

Remember

- Martel 2016 case series: Severe respiratory depression leading to hypoxia requiring airway stimulation, repositioning or intubation when olanzapine is administered via the **intravenous route in doses of 1.25mg, 2.5mg and 5mg**

And before you reach for you prescription pad…

- Intramuscularly - risk of cardiovascular and respiratory depression. It is advised that blood pressure, heart rate and respiratory rate are monitored for a minimum of four hours following IM administration and that **at least one hour has elapsed before parenteral benzodiazepines** are administered

- Caution in patients with **ileus**

Anything Unexpected?

Anorexia and Cachexia

- 3 included RCTs reported **an improvement in anorexia and cachexia** in the olanzapine compared to the control group (Nikbakhsh 2016, Navari 2010a, Mizukami 2014)

Anxiety and Depression

- Nikbakhsh 2016 - olanzapine group **anxiety and depression reduced** whilst on chemotherapy

So What's Next? What trials are underway?

- Dose response

Nagashima et al, 2015, A double-blind randomized Phase II study of olanzapine 10 mg versus 5 mg for emesis induced by highly emetogenic chemotherapy

Mukhopadhyay, 2017, Low dose vs. standard dose adjuvant olanzapine in chemotherapy induced nausea and vomiting: A prospective, randomized, double blinded, controlled study

- One RCT exploring use of olanzapine in bowel obstruction

Kaneishi, 2017, Efficacy of olanzapine for relief of nausea with incomplete bowel obstruction in advanced cancer patient: pragmatic randomized controlled trial, JPRN- UMIN000010317

- One RCT exploring chronic nausea and vomiting

Navari, 2017, Olanzapine for the Treatment of Chronic Nausea and/or Vomiting in Advanced Cancer Patients NCT03137121

Conclusion

- Oral olanzapine probably doubles the likelihood not being nauseous or vomiting during chemotherapy from 25% to 50% in adults with solid tumours
- Probably also increases somnolence and fatigue
- Not sure how low we can go with the dose

Palliative care practice

- Oncology colleagues re published systematic review
- Watching for trials from India & Asia
- Using post Levomepromazine in PC practice?

Topics

- Seizures – Dr Kiely
- Olanzapine
- Gastroparesis
- Denosumab
- Calciphylaxis

With thanks to Dr Andrew Wilcock

Palliative Drugs Update

Mirtazapine: case report

52 year old male

- progressive dysphagia → 5 days projectile vomiting
- gastric volvulus + strangulation
- emergency gastroplexy
- NG tube for persistent nausea & vomiting

Mirtazapine: case report

- no improvement with erythromycin, metoclopramide, domperidone, ondansetron

- contrast failed to flow into small bowel

- TPN → feeding jejunostomy (4 weeks after surgery)

- further 4 weeks without improvement; high NG output continued.

Johnstone M *et al*. (2009)

Mirtazapine: case report

- mirtazapine 15mg SL for low mood
- within 12h tolerating fluids, ↓ NG output
- 48h tolerating soft diet – discharged
- reviewed 3 months later, tolerating fulnl diet

Johnstone M *et al*. (2009)

Mirtazapine

(NaSSA: noradrenergic and specific serotonergic antidepressant)

Blocks receptors inhibiting mono-amine release:

- α_2-adrenergic antagonism
  - ↑ serotonin and noradrenaline release
- $5HT_{2A}$ and $5HT_{2C}$ antagonism
  - ↑ noradrenaline and dopamine release

Also antagonizes H_1- and $5HT_3$-receptors

Anti-emetic and stimulates appetite/weight gain

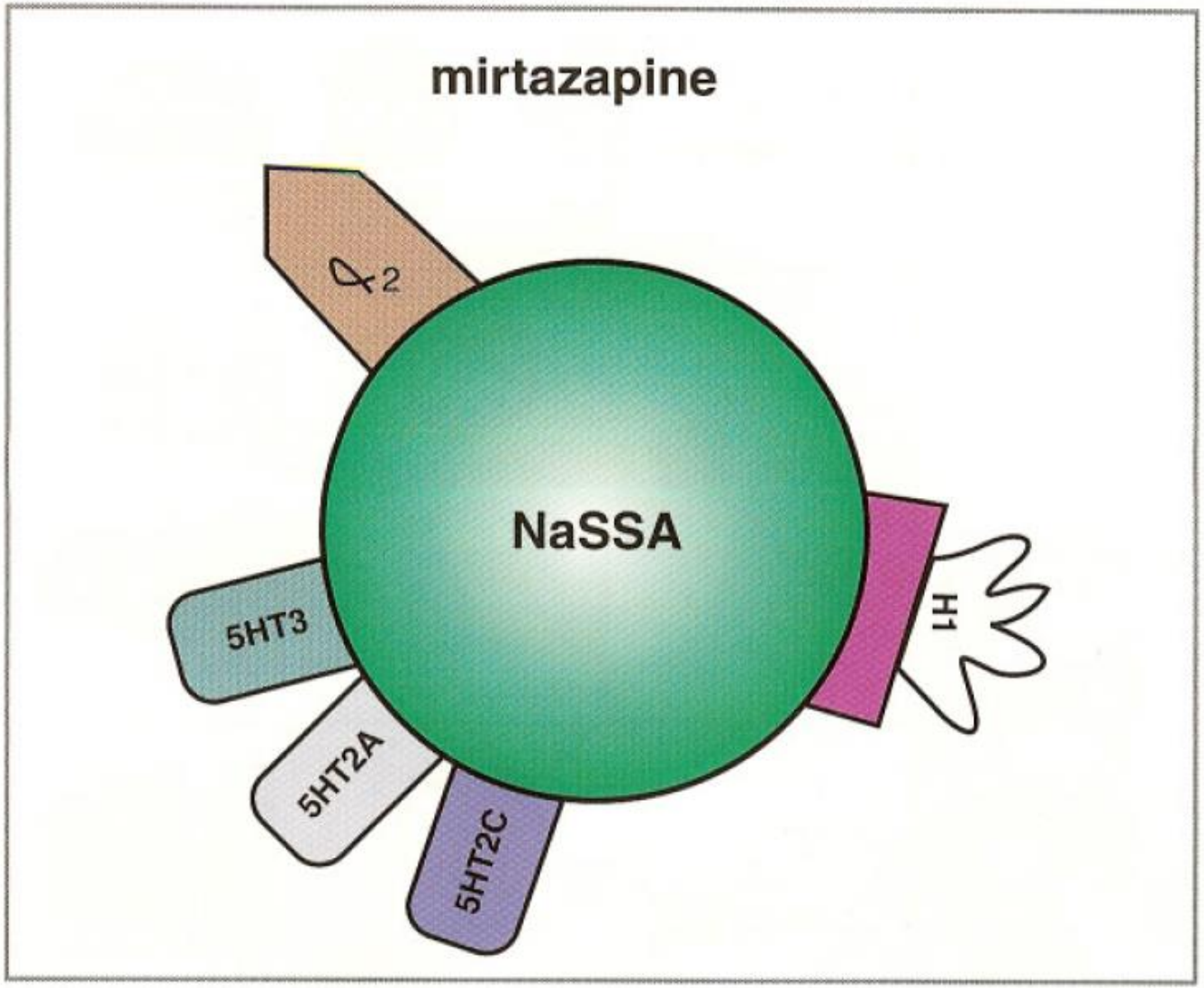


FIGURE 12-55 Icon of mirtazapine. Mirtazapine is sometimes called a noradrenergic and specific serotonergic antidepressant (NaSSA). Its primary therapeutic action is alpha 2 antagonism, as shown in Figures 12-51 through 12-54. It also blocks three serotonin (5HT) receptors: 5HT2A, 5HT2C, and 5HT3. Finally, it blocks histamine 1 (H1) receptors.

Mirtazapine

- Mechanism unclear, may include:
- anti-emetic (nausea → gastric stasis)
  - 5HT3 antagonist; effective in chemotherapy
- ↑ gastric emptying
- relaxation of gastric fundus
  - via 5HT1A receptors
  - ↑ gastric accommodation
- central ↓ in gastric sensitivity/symptoms
- change in hormone levels, e.g. ↑ ghrelin.

Kumar N *et al*. (2017)

Mirtazapine

- open label study in gastroparesis (n=30); mostly idiopathic
  - 15mg at night
  - 60–80% improved nausea, vomiting, appetite, retching
  - 20% stopped; mostly drowsiness/lethargy
  - [sedation should respond to increase in dose; for other UEs reduce starting dose to 7.5mg].

Malamood M *et al*. (2017)

Mirtazapine: anorexia

- stimulates appetite and weight gain
  - 5HT2A / H1 antagonist
  - healthy vols. mean wt gain 1.3kg / 3 weeks (15mg)
- Phase II study in cancer 15–30mg
  - ~1/4 improved appetite and wt ≥1kg / 4 weeks
- Phase III study in cancer underway
  - CI Catherine Naseef Hunter, Egypt.

Riechelmann RP *et al*. (2010)

What does this mean for palliative care?

- in gastroparesis when more usual anti-emetic approaches ineffective/unavailable may be a role for mirtazapine
- in above (and other settings), additional anti-emetic and appetite stimulating properties may be added advantages.

Clonidine

- Diabetic gastroparesis and chronic diarrhoea
- Alpha 1 adrenergic activity on enterocytes and possibly mobility

Management

- Metoclopramide
- Azithromycin (Erythroycin)
- Clonidine
- Mirtazapine

Topics

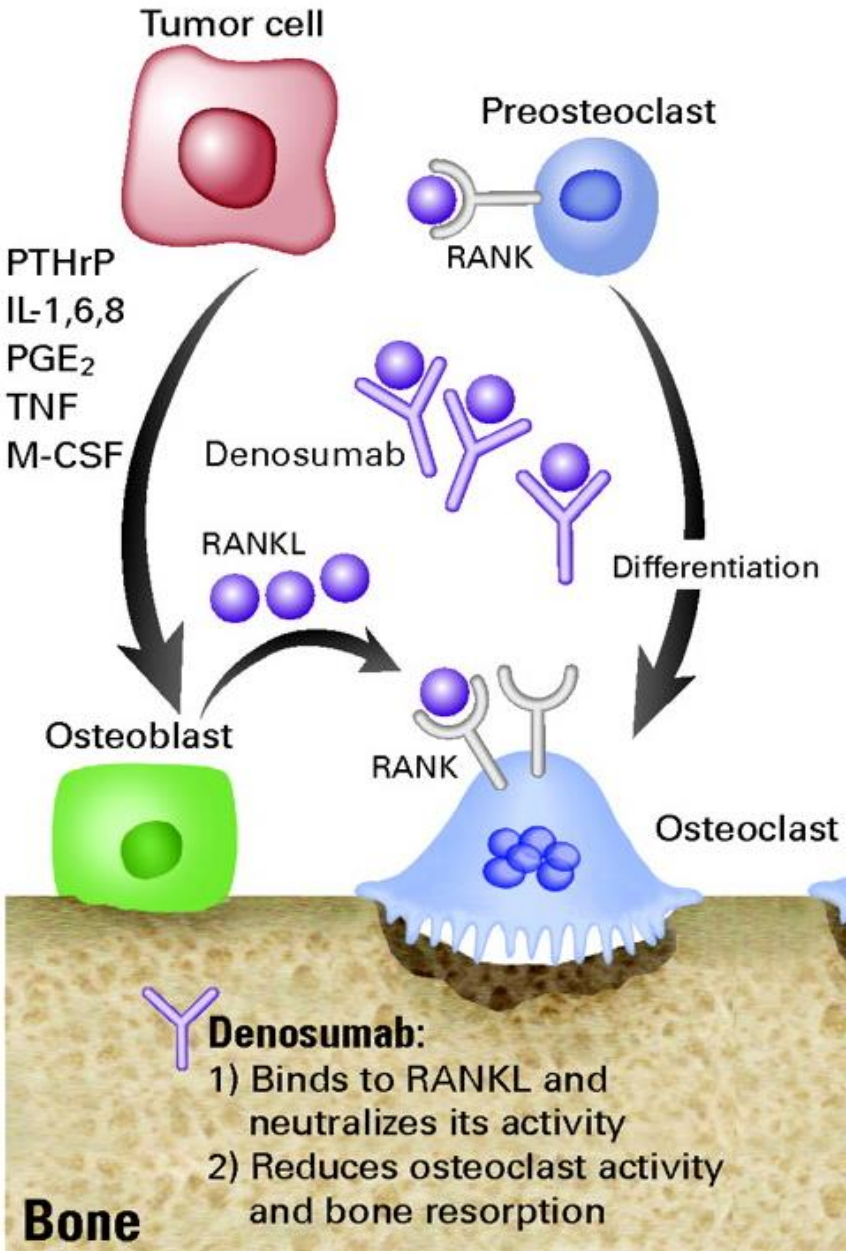
- Seizures – Dr Kiely
- Olanzapine
- Gastroparesis
- Denosumab
- Calciphylaxis

With thanks to Dr Andrew Wilcock

Palliative Drugs Update

Denosumab: Background

- human monoclonal antibody
- binds *Receptor Activator of Nuclear factor Kappa Β Ligand* (RANKL), a cytokine and member of the tumour necrosis factor superfamily
- prevents interaction between RANKL and the RANK receptor on osteoclasts
- inhibits their maturation, function and survival, and thereby bone resorption

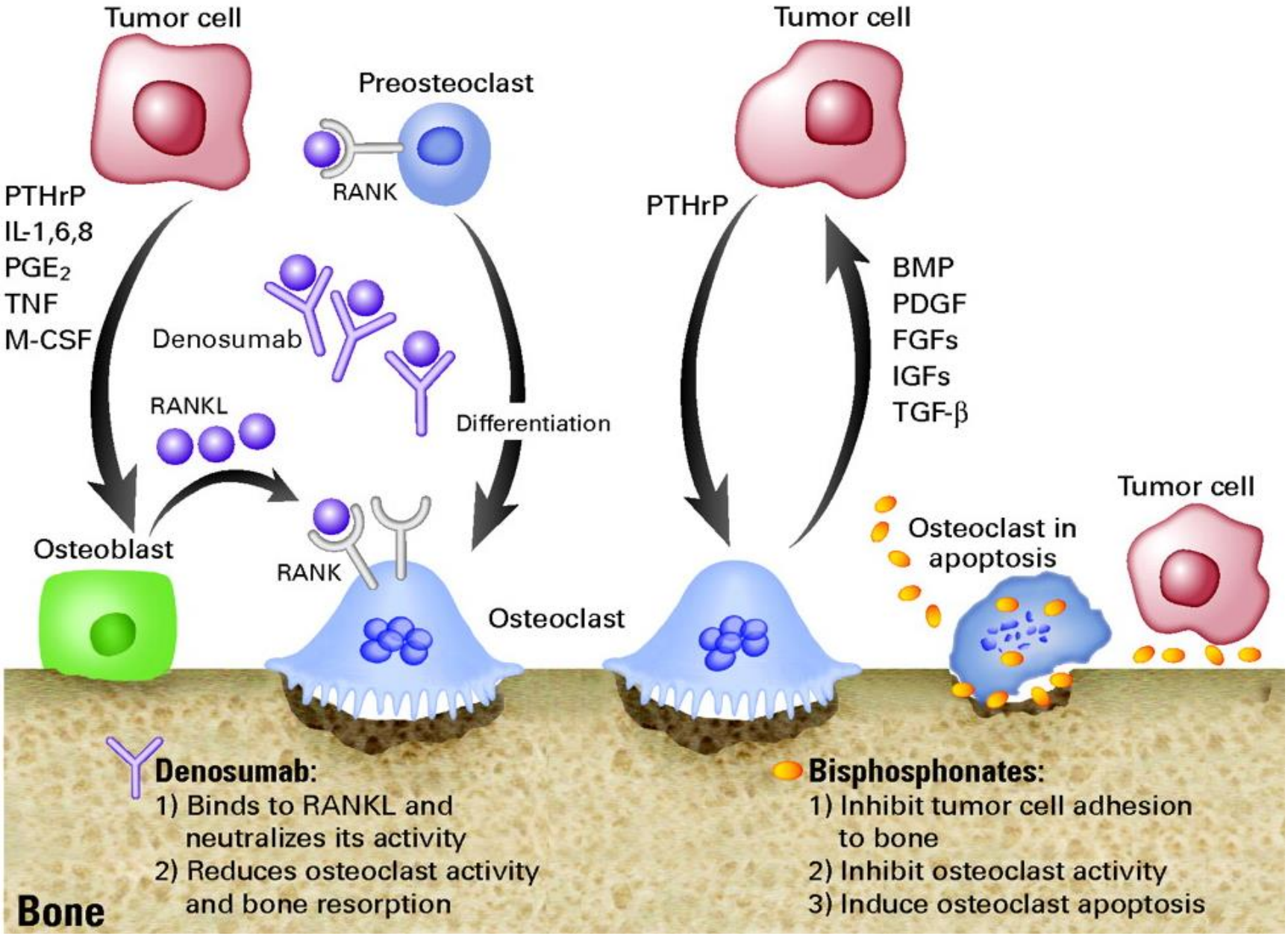

Tumor cell
Preosteoclast
RANK
PTHrP
IL-1,6,8
PGE2
TNF
M-CSF
Denosumab
RANKL
Differentiation
Osteoblast
RANK
Osteoclast
Denosumab:
1) Binds to RANKL and neutralizes its activity
2) Reduces osteoclast activity and bone resorption
Bone

Bisphosphonates: Background

- stable analogues of pyrophosphate, a naturally occurring regulator of bone metabolism
- they have high affinity for ca^{2+} ions, and bind rapidly to hydroxyapatite crystals in mineralized bone [*forms a reservoir*]
- subsequently released and taken up by osteoclasts, interfering with their function and/or inducing their apoptosis (programmed cell death).

Bisphosphonates: Background

- **zoledronic acid** most potent nitrogen-containing bisphosphonate
- inhibits the mevalonate pathway vital for normal cellular function (e.g. vesicular trafficking, cell signalling, cytoskeleton function)
- these cellular effects also extend to macrophages, reducing the production of cytokines.


Tumor cell
Preosteoclast
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M-CSF
Denosumab
RANKL
Differentiation
Osteoblast
RANK
Osteoclast
Tumor cell
PTHrP
BMP
PDGF
FGFs
IGFs
TGF-β
Tumor cell
Osteoclast in apoptosis
Denosumab:
1) Binds to RANKL and neutralizes its activity
2) Reduces osteoclast activity and bone resorption
Bisphosphonates:
1) Inhibit tumor cell adhesion to bone
2) Inhibit osteoclast activity
3) Induce osteoclast apoptosis
Bone

Denosumab vs. bisphosphonates (e.g. for prophylaxis of SRE)

	Denosumab	***Zoledronic acid***
Administration	SC injection	IVI (generally 15min)
Frequency (SRE)	Monthly (no 'reservoir' in body)	Monthly; every 3 months as effective (reservoir in bone)
Cost	120mg = £310 [£3,720 p.a.]	4mg = £10–£175 [£40–£700 p.a.]
Efficacy	+++ (cancer dependent)	++ (cancer dependent)
Tolerability	Greater risk: hypocalcaemia Similar risk: ONJ Lower risk: renal toxicity	

Specialty guidelines: solid tumours

Generally recommend the preventative use of *either zoledronic acid or denosumab* for all patients with bone metastases arising from breast or hormone-relapsed prostate cancer, and for selected patients with other solid tumours, i.e. those considered at high risk of a SRE with a likely prognosis >3 months.

Specialty guidelines: myeloma

Note that denosumab is an option, particularly in those with renal impairment, but *generally favour an IV bisphosphonate*, based on lower cost and more flexible dosing interval, e.g. zoledronic acid can be reduced to every 3 months in those without active myeloma on maintenance treatment.

[Denosumab non-inferior to zoledronic acid in delaying the time to first SRE, but associated with a lower incidence of renal toxicity (12% vs. 17%)].

What does this mean for palliative care?

PCF view

PCF notes that:

- the cost-effectiveness of the additional benefit of denosumab over zoledronic acid for the prevention of SRE is questionable
- speciality guidelines generally recommend the use of either
- the risk of discontinuation fractures is greater with denosumab than zoledronic acid

What does this mean for palliative care?

PCF view

Thus, for patients with cancer referred to a specialist palliative care service who have progressive metastatic bone disease despite monthly denosumab, unless there is severe renal impairment, *PCF* recommends considering substituting the denosumab for zoledronic acid.

What does this mean for palliative care?

PCF view (continued)

For patients with a limited prognosis, the zoledronic acid would need to be given only once, 4 weeks after the last dose of denosumab. However, if necessary, the zoledronic acid can be repeated every 3 months.

Do not just stop denosumab!

- no body reservoir (unlike bisphosphonates)
- bone turnover ↑ within 3 months, bone mineral density falls to baseline levels within 12 months and there is an ↑ risk of multiple vertebral fractures
- ? rebound ↑ activity of osteoclasts.

Do not just stop denosumab!

- thus, when used for osteoporosis, denosumab should be administered regularly, and if discontinued, a bisphosphonate used instead
- by extrapolation, the same considerations apply to its use in the cancer setting; *potentially even more important, given osteoclast stimulating effect of cancer.*

Severe hypocalcaemia

- risk 10% denosumab vs. 5% zoldedronic acid
- can be life-threatening / fatal
- follow administration guidelines, e.g.:
  - prophylactic calcium and vitamin D
  - do not give if hypocalcaemic
- be prepared to replace IV
  - added new box into denosumab monograph.

Amended advice PCF

Hypocalcaemia increases the risk of cardiac arrhythmia. IV calcium administration can cause hypotension, cardiac arrhythmia and precipitate digoxin toxicity, and continuous heart rate monitoring is required in patients at higher risk of cardiotoxicity, e.g. those with ECG changes, cardiac disease or taking digoxin.[*NUH guidelines*] Recommendations on the need for continuous ECG monitoring vary, ranging from the ideal of its routine use to, as a minimum, in the high risk group above.[*ref Turner; UKMI; NUH guidelines*] Stop or slow the infusion if bradycardia or hypotension occur.

Denosumab for ‘refractory’ tumour-induced hypercalcaemia (TIH)

- bisphosphonates very effective
  - [remember forced diuresis/mithromycin/calcitonin?]
- generally, unresponsive hypercalcaemia part of terminal decline
- occasionally, main problem for a patient with a reasonable performance status.

Denosumab for ‘refractory’ TIH

- small study, n=33
- mostly breast, myeloma, neuroendocrine, NSCLC, renal cancers
- hypercalcaemia = corr. calcium >3.1mmol/L; median 3.4mmol/L
- despite prior bisphosphonate use; median (range) 4 (1–41) months
- last dose within 8–30 days; median 17 days.

Denosumab for ‘refractory’ TIH

- give 120mg SC every 4 weeks; *give additional 120mg SC doses on days 8 and 15 of the first month of therapy*
- i.e. usual regimen with initial ‘loading’ to reach effective serum concentrations quicker (demonstrated in other setting)
- discontinued if calcium >3.1mmol/L after 4 doses.

Denosumab for ‘refractory’ TIH

Primary endpoint

- proportion of responders (calcium ≤2.9mmol/L) within 10 days of first dose

Denosumab for ‘refractory’ TIH

response: 9 days

- duration of response: 104 days

- to complete response: 23 days
  - duration of complete response: 34 days.

Denosumab for ‘refractory’ TIH

- symptoms improved (~1/2) or resolved (~1/3)
- 2 patients had asymptomatic grade 2 hypocalcaemia (1.75–2mmol/L)
- [*PCF monograph includes Box on treatment*]
- 4 nausea (potentially treatment related)
- 1 cardiac arrest (possibly treatment related)
- 1 colitis (possibly treatment related).

What does this mean for palliative care?

- denosumab is a reasonable treatment option for TIH refractory to bisphosphonate therapy.

With thanks to Dr Smeeta Sinha

Calciphylaxis 2017

Case

AS, 41 Female

- Admitted May 2012 with lower abdo pain and back pain

- Background
  - End stage renal failure on maintenance HD since 2009
  - Primary disease – hypertension
  - T2 DM – on insulin
  - OSA
  - Atrial fibrillation – commenced 6 months previously (CHADSVASC = 3)
  - Morbid obesity BMI 70

- Medications
  - Omeprazole 20mg OD
  - Gliclazide 80mg OD
  - Atorvastatin 20mg nocte
  - Bisoprolol 5 mg od
  - 1 alpha calcidol 0.25mcg 3x/week
  - Warfarin
  - Co-codamol PRN
  - Insulin

Clinical Course

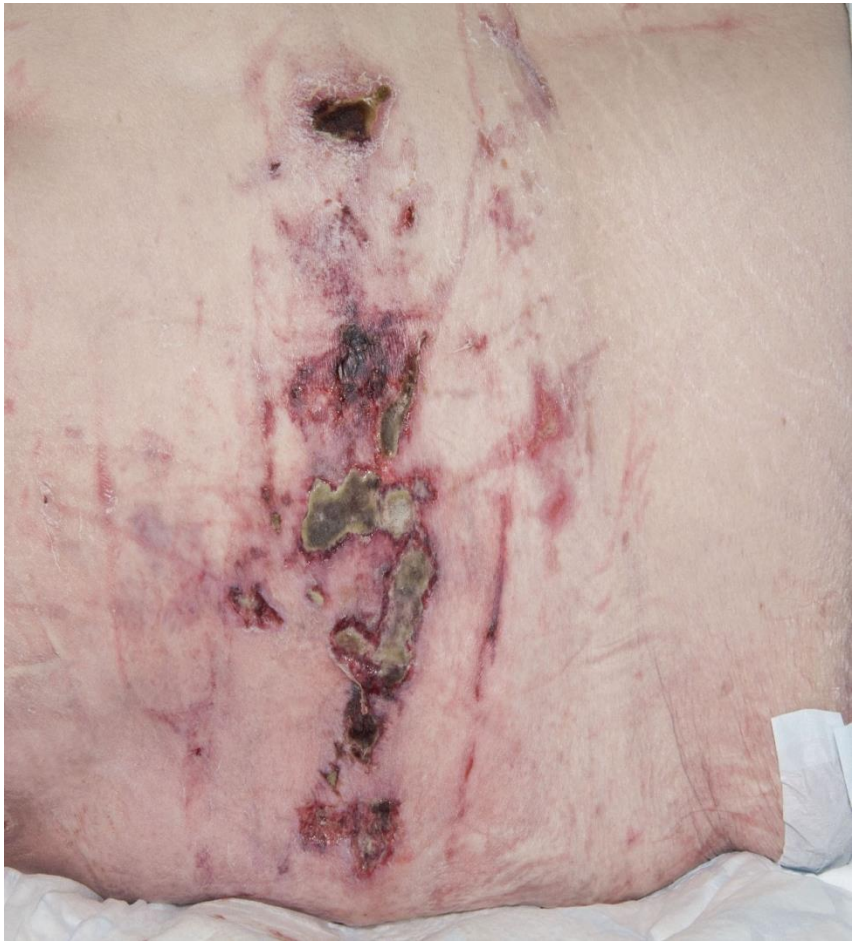
- Investigations:
  - CT Spine: complete destruction of superior L4 and inferior L3 end plates
  - Blood cultures: E-coli
- Management:
  - 3 months of abx, monitoring with x-rays and CRP
  - Recurrent urinary sepsis requiring antibiotics
  - Complicated by clostridium difficile treated with oral vancomycin
  - Progressive immobility requiring extensive rehab

Clinical Course

September 2012
(4 months after admission)

- Bruising noted
- Rapid deterioration with ulcer formation

- Skin biopsy confirmed calciphylaxis



Epidemiology

- Predominantly ESRD
  - ≤ 1% prevalence
  - Mortality 60 - 80%
- Non-uraemic calciphylaxis
  - Primary hyperparathyroidism,connective tissue disorders, type 2 diabetes mellitus, alcoholic liver disease, malignancy
  - Most associated with normal Ca, P, low/normal PTH
  - Mortality 50%

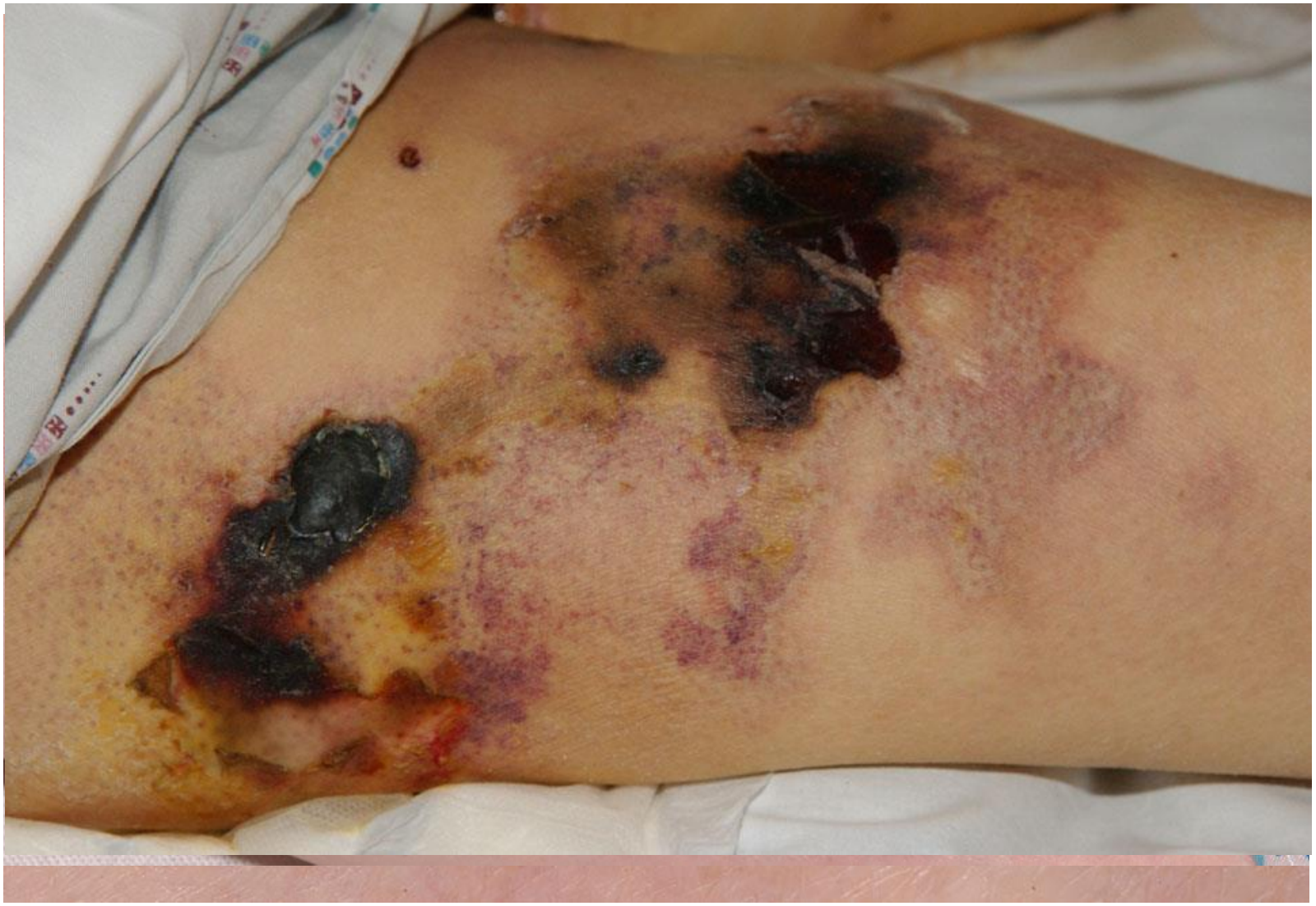
Brandenburg J Neph 2011, Nigwekar *et al* cJASN 2008

Clinical features

- Tender indurated plaques or livedo reticularis
- Palpable subcutaneous deposits (calcium)
- Surrounding pallor or ecchymosis with associated hyperaesthesia.
- SEVERE PAIN
- Ulceration is probably a late presentation

Nigwekar *et al* cJASN 2008

Skin lesions in calciphylaxis



Diagnosis

- Clinical
- Histology
  - False negative results
  - Formation of new, non-healing ulcers
  - Small arteries/arterioles
  - UK Calciphylaxis Study >70% tissue diagnosis*

Fischer *et al Hum. Pathol.* 1995; *Sinha UK Calciphylaxis Study 2017

Risk factors

- Caucasian
- Female
- Co-morbid conditions
  - *CKD*
  - *Diabetes*
  - ***Obesity (81%)***
  - *Liver disease*
  - *Malignancy*
  - *Hypercoagulable states (?)*
- **Dialysis**
  - *Dialysis vintage*
  - *Peritoneal dialysis*

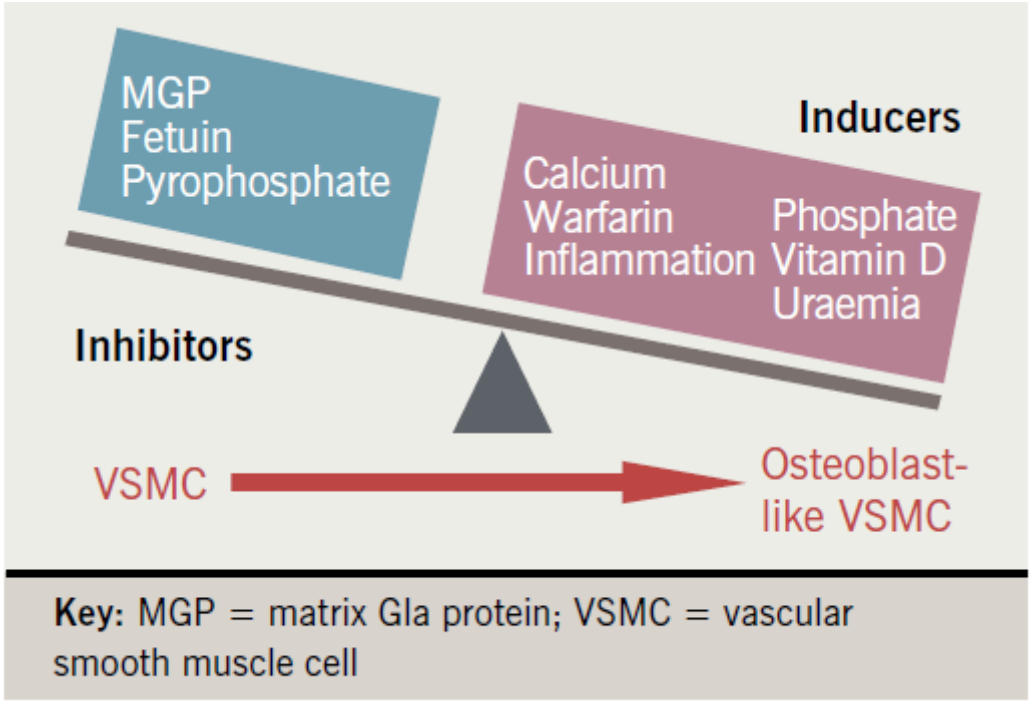
- Medications
  - ***Vitamin K antagonists (Warfarin)***
  - *Vitamin D*
  - *Calcium-containing binders*
  - *Steroids (non-uraemic)*

- Abnormal bloods
  - ↑ *phosphate*
  - ↑ *calcium*
  - ↑ *PTH*
  - ↓ *albumin*
  - ↑ *ALP*
  - ↑ *aluminium*
  - ↓ *protein C & S*

Natural history

- ***German Calciphylaxis Registry***
  - Some apparent improvement in outcomes
  - Median survival 548 days
  - Earlier identification
  - Improved wound care and reduction in sepsis
  - Improved management of risk factors
- ***UK Calciphylaxis Study***
  - 55.9% female; 94.4% caucasian
  - Median age 57 (51-66) years
  - Median BMI 34.6 (26.6-37.8)
  - Most common lesion locations were the lower extremities (57.7%), thighs (32.4%) and abdomen (16.9%)
  - Low serum albumin and warfarin use associated with worse outcomes

Pathophysiology of VC



Key: MGP = matrix Gla protein; VSMC = vascular smooth muscle cell

Sinha *et al BJC* 2008

Why did AS develop calciphylaxis?

- Predisposition:
  - Started haemodialysis resulting in pertubations in calcium, phosphate handling and perhaps early remodelling of VSMC
  - Started warfarin resulting in loss of MGP function

- Triggers:
  - Episodes of hypercalcaemia
  - Chronic inflammation/recurrent sepsis resulting in loss of fetuin function

Hyperbaric oxygen

Rogers *et al* reviewed literature

34 patients treated → 23 recovered

- Counteracts tissue hypoxia
- Improved wound healing
  - Increasing angiogenesis
  - Fibroblast proliferation and laying down of collagen
  - Increase bactericidal effects in infected wounds by improving neutrophil function
- Promotes arteriolar vasoconstriction and reduces oedema and ischaemia/reperfusion injury
- Higher oxygen tension is toxic to some organisms (*Clostridia spp*)

Rogers *et al* Semin Dial 2007

Reduce calcifying factors

- Increase dialysis frequency
- Switch from PD to HDx[1]
- Low calcium dialysate
- Stop Vit D & calcium supplements

SChlieper *et al* Nat Rev 2009 [1]Fine *et al* PDI 2008

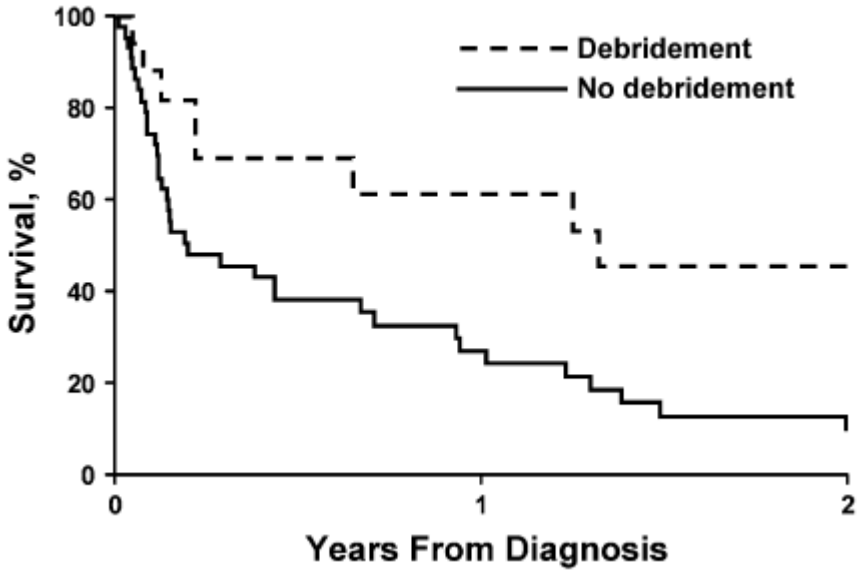
PD conversion to HD

- Fine *et al* Manitoba, Canada
- Prospective data on calciphylaxis cases
- 1998 to 2006: 59 patients
  - 54 on PD; 4 HDx; 1 CKD
  - Reduction in incidence in latter 3 years of study
    - 4.5/100 patient years in 1999 – 2002
    - 1.3/100 patient years in 2003 - 2006
    - Attributed to reducing use of calcium salts
- 13 patients converted to Hdx - all improved

Schlieper *et al* Nat Rev 2009

Surgical debridement

- 63 with f/u
- 17 underwent debirdement
- Significant survival advantage (p = 0.008)
  - *61.6% vs 27.4%*



Weenig *et al*

Reduce calcifying factors

- Increase dialysis frequency
- Low calcium dialysate
- Stop Vit D & calcium supplements
- Administer bisphosphonate (caution in adynamic bone disease)
- Parathyroidectomy for hyperparathyroidism
- Cinacalcet in cases of hyperparathyroidism

Schlieper *et al* Nat Rev 2009

Increase calcification inhibitors

- Stop vitamin K antagonists
  - Improves MGP action
  - Give vitamin K
- Treat infections & pro-inflammatory conditions
  - enables fetuin-A levels to increase

Schlieper *et al* Nat Rev 2009

Medical therapy

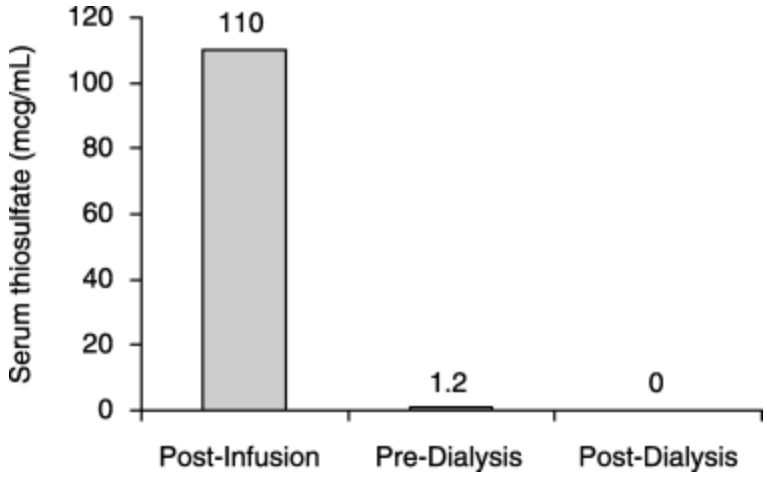
- Sodium thiosulphate (not funded via NHS England)
- Cinacalcet
- Bisphosphonates
- Hyperbaric oxygen
- Vitamin K

Schlieper *et al* Nat Rev 2009

Prevent calcium-phosphate precipitation

Sodium thiosulphate ($Na_2S_2O_3$)

- Reducing agent
- Mechanism of action
  - Formation of calcium-thiosulphate complexes (highly soluble)
  - Reduces antioxidant activity
- Poor intestinal absorption → IV administration
- Rapidly removed in urine:
  - half life 15 minutes
- Removed by HDx
- Post HDx (5g) -
  - half life 478 minutes[2]



Raymond *et al* Am. J. Health Syst. Pharm 2008; [2]Brucculeri *et al* Semin Dial 2005

Sodium thiosulphate ($Na_2S_2O_3$)

- Numerous case reports
- No clinical trials in calciphylaxis
- Pilot study 86 maintenance HDx patients[1]
  - CAC score >300 randomised
  - Thiosulphate for 4 months
  - Progression in 23% of treatment group vs 63% control
- Optimum dose → ?
- 25 g (over 30 – 60 minutes) post HDx 3 x/week
- Can give IP (but preferable to convert to HDx)[2]
- Duration 6 weeks to 34 months

Raymond *et al* Am. J. Health Syst. Pharm 2008;[1]Adirekkiat *et al NDT* 2010; [2]Brucculeri *et al* Semin Dial 2005

Sodium thiosulphate ($Na_2S_2O_3$)

- Meade *et al*
  - 16 patients treated with sodium thiosulphate
  - 1 patient unable to tolerate
  - 14/15 improvement noted
  - 2 complete resolution
- 62 reported patients treated with sodium thiosulphate
  - 82.2% (51/62) patients improved
  - **Publication bias**
- Acceptable safety profile
  - Some concerns re: long-term effects on bone health
- Short term adverse effects[2]
  - Nausea, vomiting, headache, metabolic acidosis

[1]Meade *et al* ASN 2008 [2]Schlieper *et al* Nat Rev 2009

Sodium thiosulphate ($Na_2S_2O_3$)

- Noureddine *et al*
  - Retrospective medical record review (5 years, 4 hospitals)
  - 14 patients treated with sodium thiosulphate
  - pain decreased in 71% of patients
  - 70% had an improvement in their lesions
  - Poor response associated with advanced skin lesions, dialysis vintage, obesity and lower total dose sodium thiosulphate
  - **71% mortality rate despite treatment**
  - **50% of patients still died within 6 months.**

[1]**Nouredine *et al Clin* Clin Neph 2011**

Summary to date

- Usually seen in ESRD
- Associated with high mortality rates (60 -80%)
- Characterised by very painful cutaneous non healing ulcers
- Due to small vessel calcification
  - Multifactorial causes of calcification
- Biopsy can be helpful for diagnosis

- Treatment often requires multiple approaches
  - Supportive
  - Good wound care, debridement & surgical
  - Advanced care planning

- Medical management
  - Remove exacerbating factors
  - Treat infections promptly
  - Optimise dialysis

- Specific drug therapies
  - Sodium thiosulphate
  - Also consider bisphosphonates, vitamin K, cinacalcet and hyperbaric oxygen