Peripheral Neuropathy

Case presentation

Maxine Rudkin
Nottingham City Hospital
October 2007

Why?

"Bortezomib has been chosen specifically because it is the most significant therapy discovered for myeloma in over a decade with increasing use and relevance to current clinical practice"

(International Myeloma Foundation 2006)

What is velcade?

- Cytotoxic agent called ‘Proteasome inhibitors’
- Velcade temporarily blocks the proteasome causing a build up of waste proteins causing confusion and cell death
- Myeloma cells are 100 to 1000 times more sensitive to velcade than healthy cells

Current use of velcade

Indicated for:

- **Progressive myeloma (at least one prior therapy and already had or unsuitable for BMT)**
- **First relapse and transplant not a current option**

Recognising progression and relapse:

- **Increasing paraprotein level**
- **Bone pain**
- **Hypercalcaemia**
- **Decline in renal function**
- **Anaemia**
- **infection**

Aim of velcade

- Identified role for the treatment of patients at first relapse
- Clinical evidence for the use of velcade (increased activity with dex) as a treatment for second relapse
- Maximise quality of life
- Increase duration of survival
- Disease control

(Morgan 2005)

Velcade combination therapy

- Dexamethasone (20% greater response than single agent velcade) (Morgan 2005)
- PAD

Trials

- Melphalan
- Vista
- Anti-IL-6 monoclonal antibody

Associated therapies

- Dexamethasone
- Allopurinol
- Lansoprazole
- Co-trimoxazole
- Metoclopramide
- Aciclovir

Velcade administration

- Velcade is usually administered on day 1,4,8 and 11 followed by 1 week rest period
- Velcade is administered over 3-5 seconds
- Velcade may be directly injected into a peripheral line by IV bolus or injected into an infusion port
- Flush with normal saline to ensure full dose
- Infusion reactions and infusion-site reactions are uncommon
- Velcade is not a vesicant

(Janssen Cilag 2005)

What is peripheral neuropathy?

- Peripheral neuropathy is damage to peripheral nerves
- It may be sensory and/or motor
- Peripheral neuropathy often affects the arms and hands, and/or legs and feet

Common signs;

- Muscle weakness
- Pain
- Numbness
- Loss and/or change of sensation
- Increased sensitivity
- Paralysis
- Lack of co-ordination
- Loss of ability

Cancer Bacup (2006)

Autonomic nerves

- Control heart rate, blood pressure and digestion.

- Organ dysfunction
- Digestion
- Blood pressure

Severe:

- Breathing
- Organ failure

- More research is required to look at autonomic neuropathy associated with bortezomib

Case Study

49 year old lady presented to GP with painful swollen hands in November 1998.

- Referred to haematologist; myeloma diagnosed. Neurology assessment- normal

Treatment;

- CVAD and PBSCT (auto) May 1999 – CR
- Jan 2000 "some pins and needles in fingers" ? Vincristine, observe for now
- May 2001 "pins and needles in hands"
- May 2002 – severe night cramps – try tonic water ?quinine
- Jan 2003 – relapse – Thalidomide + Cyclophosphamide
- April 2004 – 2nd PBSCT (auto) - CR
- March 2006 = relapse – BM trial
- March 2006 = thrombocytopenia + neutropenia; velcade dose reduced
- May 2006 – "neuropathy ++" – velcade deferred (CR)
- June 2006 – PN grade 2/3 "pain in soles" Velcade discontinued, 2 cycles completed
- July 2007 – relapse; velcade(reduced dose)+dexamethasone – Grade II PN at baseline

Thalidomide

"PN can be irreversible if the drug is not promptly withdrawn and therefore patients must be carefully monitored"

(Baccadoro, Blade, Attal, Palumbo 2005)

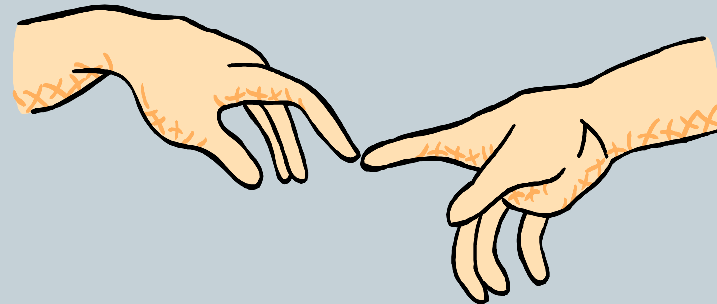
	time of appearance	**frequency**
Neuropathy	>6 months	50%

Dimopoulos et al. (2004)

Adverse events profile for velcade

Phase II Clinical Trial (N=311)

Nausea	57%
Diarrhoea	57%
Constipation	42%
PN	**36%**
Vomiting	35%
Thrombocytopenia	35%
Pyrexia	35%
Anorexia	26%
Headache	26%
Anaemia	23%
Neutropenia	19%
Pain in limb	16%
Arthralgia	12%



Richardson et al (2005)

Quality of Life

"Neurotoxicity affects the patient not only physically, but also functionally, psychosocially, and spiritually, and in turn can affect the family as well"

Nielsen Brant (2002)

Quality of life

What adverse effects does peripheral neuropathy have on patients quality of life?

Patients Perspective

- "I can't do my patchwork and sewing anymore"
- "Difficulty getting in and out of bungalow" (4 steps)
- "I feel like I am standing on lumps"
- "I can only manage to get halfway around the supermarket with support of a trolley, then my husband has to take over"
- "hot aches in feet that make me cry – nothing works to relieve it"
- "severe night cramps that last all night approx. 3 nights per week"
- "I cannot test the temperature of my bath water" (previous burn to bottom)
- "I cannot cut my toe nails due to numbness, I have previously cut them too short"

Assessment

"Assessment of the severity of chemotherapy induced neuropathy is difficult. It may be questioned whether clinical neurological signs (the doctors perspective) are objective and important enough for accurate neuropathy grading"

"A study including 15 doctors and 68 patients found priority ratings of PN differed substantially between doctors and patients for several items"

Postma et al (1999)

"Peripheral Neuropathy is often more frequent and distressing for patients than generally recognised"

(Smith et al 2006)

Assessment

"Nurses play an important role in the early detection of and intervention for neurotoxicity, the success of treatment, and the patients quality of life"

(Nielsen, Brant 2002)

"Many of the symptoms of PN are subjective in nature so the assessment should be based, at least in part, on patient self-report data"

(Morgan et al. 2005)

Nursing role

Nurse to take on more active role in velcade administration and toxicity assessment. Leading to:

- Improved patient education
- Improved side-effect management
- Maintain therapeutic dose of velcade
- Reduced incidence and severity of PN
- Improved patients quality of life
- Improved patients velcade journey

Assessment tools

1. Do Haematology Centres use peripheral neuropathy assessment tools?
2. Are these performed by nurses/doctors?

WHO Performance Status

0 – you are fully active and more or less as you were before your illness

1 – you cannot carry out heavy physical work, but can do anything else

2 – you are up and about more than half the day; you can look after yourself, but are not well enough to work

3 – you are in bed or sitting in a chair for more than half the day; you need some help in looking after yourself

4 – you are in bed or a chair all the time and need a lot of looking after

NCI Common Toxicity Criteria Version 2

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neuropathy - motor	normal	Subjective weakness but no objective finding	Mild objective weakness interfering with function, but not interfering with ADL	Objective weakness interfering with ADL	Paralysis
Neuropathy - sensory	normal	Loss of deep tendon reflexes or parasthesia but not interfering with funtion	Objective sensory loss or parasthesia, interfering with function but not with ADL	Sensory loss or parasthesia interfering with ADL	Permanent sensory loss that interferes with function

Velcade Neurotoxicity Assessment Scale

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have numbness or tingling in my hands	0	1	2	3	4
I have numbness or tingling in my feet	0	1	2	3	4
I have discomfort in my hands	0	1	2	3	4
I have discomfort in my feet	0	1	2	3	4
I have joint pain or muscle cramps	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I have trouble hearing	0	1	2	3	4
I get a ringing or buzzing in my ears	0	1	2	3	4
I have trouble buttoning buttons	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
I have trouble walking	0	1	2	3	4

Side effect management – dose modification

Grade 3 non-haematological or grade 4 haematological toxicity

- **Withhold velcade until toxicity resolves and then reintroduce at a 25% lower dose**
- **1.3mg/m² reduce to 1.0 mg/ m²**
- **1.0mg/m² reduce to 0.7mg/ m²**

PN

Grade 1	**No action**
Grade 1 with pain or grade 2 (interfering with function but not with A o L)	**Reduce to 1.0 mg/ m2**
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	**Withhold velcade until toxicity resolved Reinitiate at lower dose and once per week.**
Grade 4 (permanent sensory loss that Onterferes with function)	**Discontinue velcade**

Treatment

"Dose reduction and treatment discontinuation are the main effective strategies to overcome, or at least reduce, neurological toxicity"

(Baccardo, Blade, Attal, Palumbo 2005)

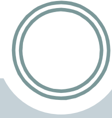
Velcade

“PN can be a dose limiting adverse event; therefore patients should be monitored frequently for symptoms of neuropathy”

“Early detection and appropriate dose/schedule modification may prevent the progression of neuropathy”

Ortho-biotec (2006)

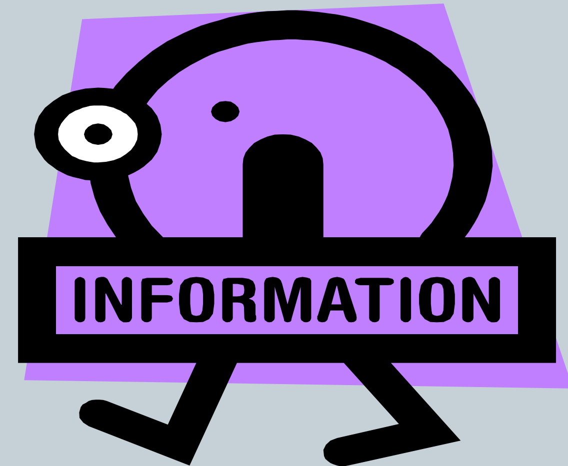
Treatment/Interventions



What interventions or treatments are used for peripheral neuropathy in clinical practice?

Treatment/Interventions

- Prevention or early detection
- Education;
  - injury prevention
  - signs and symptoms to report
- Pain management
- Complementary therapies ?
- Spinal cord stimulation ?
- Vitamins ?
- Magnesium and potassium supplements
- Gabapentin
- Amitryptiline
- Sertraline
- 5% lidocaine patches



- Patient education for signs and symptoms
- Blood products
- GCSF
- Anti-emetics
- Laxatives or antidiarrhoeal medication
- Analgesia / Gabapentin / Amitryptyline
- Monitor blood pressure
- Ted stockings / review anti-hypertensive meds
- Rest, nutrition, hydration and exercise
- Review hypotensive medication
- Review diabetic medication

Patient velcade journey

Before nurse led telephone clinic			After nurse led telephone clinic	
Day 1			**3 days prior to day 1**	
FBC			**FBC at day case or GP**	
Attend clinic			**Telephone assessment**	
Velcade prescribed			**Velcade prescribed**	
Find pharmacist to screen prescription			**Prescriptions screened**	
Take prescription to cytology lab			**Day 1**	
Wait for velcade to be made			**Velcade and oral medication made in advance**	
Wait for oral medication			**Attend clinic**	
Administration of velcade			**Administration of velcade**	

Nurse led telephone assessment

Advantages

Less waiting time
Assist pharmacy planning
Less nursing time on day 1
Hospital transport
?? Improved assessment and documentation of toxicity
?? Improved management of toxicity
?? Improved QoL
?? Shorter consultant clinic time

Disadvantages

Two visits
Need a telephone
Increased time on day –3
?? Drug wastage
?? Increased side effects
Language barriers
Cannot be used for clinical trials

Response to velcade

- The majority of responses are detectable within 2-3 cycles (Jagganath et al 2004 and Richardson et al 2003, 2004)
- Therefore consider stopping treatment after 3-4 cycles if no response is seen (Morgan et al 2005)

Velcade response scheme

- Velcade monotherapy is recommended by NICE as an option for the treatment of progressive myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, BMT.
- Response to velcade is measured using serum M-protein after a maximum of 4 cycles
- Treatment is discontinued in people who have less than 50% response (that is, less than partial response)
- Manufacturer rebates the full cost of velcade for people who have less than partial response

Cost of velcade

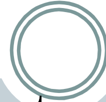
- £14,000 per treatment (8 cycles)

- 1 vial = £762.38 (2005)
- Approx. 8.5 patients per million population may be suitable for treatment (Morgan et al 2005)
- Approx £120,000 per million of population (Morgan et al 2005) – this ignores savings from stopping non-responding patients early.

Nursing role

- **Listening**
- **Proper and safe administration of velcade Outpatient setting**
- **Individual care**
- **Nurses must have appropriate knowledge and updates**
- **Often the first to identify signs of side effects**
- **Patient education**
- **Support and holistic care with referral to MDT as required**
- **Organisation of care and supportive care**
- **Patient advocate**
- **Information and patient empowerment**

Patient information and education



- Informed choice of treatment options
- Improved understanding and compliance
- Patients vary in the level of information they wish to be given
- A balanced view of the benefits and side effects should be given
- Written information
- Local and national information services
- Point of contact
- Take part in trial or not?
- Anticipated side effects and careful patient assessment can lead to effective symptom management Administration of all doses is dependent on effective symptom control

Conclusion

Chemotherapy-induced PN may seriously compromise patients quality of life. Therefore it is important to be able to assess PN in a valid and reliable manner, both in clinical trials and in clinical practice, where the treatment is known or suspected to induce PN"

(Postma et al 2005)

"PN has important clinical relevance as a major dose-limiting adverse effect of treatment which may hinder or patients receiving the therapeutic dose"

(Richardson et al. 2003)

"In cancer treatments, sometimes the benefits of taking the drug to cure or control a cancer may outweigh the discomfort and inconvenience of the neuropathy it is causing. However, if the neuropathy is severe patients may feel that the disadvantages outweigh the benefits"

Cancer Bacup (2006)

Conclusion

- Nurses are in the best position to inform and educate patients about the side effects
- Nurses will see patients on days 1, 4, 8 and 11 whereas Doctors will usually only see patients on day 1
- Nurses are in a key position to identify signs and symptoms of toxicity
- Supportive therapies and strategies for side effect management can prevent worsening of these symptoms, thereby avoiding dose reductions and treatment delays (Colson et al 2004).
- reducing incidence and severity of toxicty can improve patients quality of life Caress (2003)
- Patient inclusion in treatment decisions and assessment is also essential to identify that the benefit of treatment is worth the discomfort and inconvenience of any toxicity (Postma, Aaronson, Heimans, Muller, Hildebrand, Delattre, Hoang-Xuan, Lanteri-Minet, Grant, Huddart, Moynihan, Maher, Lucy 2005).

References

Baccadoro M., Blade J., Attal M., Palumbo A (2005) The future role of thalidomide in MM Acta Haematol 114 supple. Pp.18-22

Cancer Bacup (2006) Peripheral Neuropathy www.cancerbacup.org.uk

Dimopoulos M., Eleutherakis-Papaiakovou V. (2004) Adverse effects of thalidomide administration in patients with neoplastic diseases The American Journal of Medicine 117(7) pp.508-515

Morgan G., Davies F., CavenaGH j., Jackson G. (2005) Position statement on the use of bortezomib in multiple myeloma on behalf of the United Kingdom Myeloma Forum (UKMF) and the Haematology Oncology Task Force of the British Committee for Standards in Haematology

Nielsen E., Brant J. (2002) Chemotherapy-Induced Neurotoxicity: Assessment and interventions for patients at risk American journal of Nursing 102 pp.16-19

Ortho Biotec(2006) Velcade Q&A

Postma T., aaronson N., Heimans J., Muller J., Hildebrand J., Delattre J., Hoang-Xuan K., Lanteri-Minet M., Grant R., Huddart R., Moynihan C., Maher J., Lucey R. (2005) The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: The QLQ-CIPN20 European Journal Of Cancer 41(8) pp.1135-1139

Postma T., Heimans J., Aaronson N., Grant R., Huddart R., Maher J., Hildebrand J., Lanteri-Minet M., Delattre J. (1999) The impact of chemotherapy induced peripheral neuropathy on quality of life Journal of Neurology, Neurosurgery and Psychiatry 67(6) pp.838-839

Richardson P. Et al. (2005) Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma The New England Journal of Medicine 352(24) pp2487-2498

Smith A., Wisloff F., Samson D. (2006) Guidelines on the diagnosis and management of multiple myeloma 2005 British journal of Haematology 132(4) pp.410-451