Prävention and Behandlung von Nebenwirkungen der Myelomtherapie

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Qualität der Betreuung in onkologischen Schwerpunktpraxen

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Round 1</th>
<th>Round 2</th>
<th>Compare Round 1 v 2</th>
<th>Variation Among Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were pain addressed?</td>
<td>70 46 71 48</td>
<td>62 44 60 56</td>
<td>2.658 .10</td>
<td>20.6 12.6 0.048</td>
</tr>
<tr>
<td>Was G-CSF given per guideline?</td>
<td>36 94 36 50</td>
<td>141 184 97 112</td>
<td>6.306 .01</td>
<td>0.88 20.4 .002</td>
</tr>
<tr>
<td>Were serotonin antagonists given per guideline?</td>
<td>141 184 88 97</td>
<td>141 184 88 97</td>
<td>2.622 .11</td>
<td>60.97 27.4 .001</td>
</tr>
<tr>
<td>Were corticosteroids added per guideline?</td>
<td>123 121 60 50</td>
<td>123 121 60 50</td>
<td>3.917 .048</td>
<td>37-100 22.6 .001</td>
</tr>
<tr>
<td>Was a pathology report available?</td>
<td>250 96 395 96</td>
<td>250 96 395 96</td>
<td>0.003 .95</td>
<td>94.97 8.1 .03</td>
</tr>
<tr>
<td>Was staging completed?</td>
<td>291 62 395 97</td>
<td>291 62 395 97</td>
<td>N/A* - 78.93 16.4 .012</td>
<td></td>
</tr>
<tr>
<td>Were flow sheets used when chemotherapy was given?</td>
<td>158 100 324 100</td>
<td>158 100 324 100</td>
<td>N/A - None N/A N/A</td>
<td></td>
</tr>
<tr>
<td>Was a signed consent for chemotherapy on the chart?</td>
<td>158 71 324 16</td>
<td>158 71 324 16</td>
<td>N/A - 270.6 0.001</td>
<td></td>
</tr>
<tr>
<td>In the absence of a signed consent, was consent documented?</td>
<td>46 N/A 136 80</td>
<td>46 N/A 136 80</td>
<td>N/A - 247.2 0.001</td>
<td></td>
</tr>
<tr>
<td>Was some form of consent documented?</td>
<td>158 N/A 324 92</td>
<td>158 N/A 324 92</td>
<td>N/A - 62-100 73.7 .001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: G-CSF, granulocytic growth factors; N/A, not applicable.
* The definition of "staging" was expanded to include any statement of "metastatic" or "advanced" disease.
† The question was changed between rounds to allow clear distinction between a formal written consent form and a notation that the practitioner had discussed chemotherapy and the patient consented.

Neuss MN et al., JCO 2005
Häufige Nebenwirkungen 'neuer' Myelom Medikamente

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Thalidomide</th>
<th>Bortezomib</th>
<th>Lenalidomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy</td>
<td>+++</td>
<td>+++</td>
<td>(+)</td>
</tr>
<tr>
<td>Constipation</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Bone Marrow Suppression</td>
<td>+</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Thromboembolic Complications</td>
<td>+++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>+++</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

Anatomie eines Neurons

1. Small fibres
2. Afferent sensory fibres
3. Efferent motor fibres
4. Neural cell body
5. Myelum
Symptome der Polyneuropathie

- **Sensorische Symptome**
  - Verminderte Empfindlichkeit, Taubheitsgefühl
  - Parästhesia, Hyperästhesie
  - Neuropatischer Schmerz
  - Zittern
  - Gefühllosigkeit

- **‘Motorische’ Symptome**
  - Schwäche

- **‘Autonome’ Symptome**
  - Blutdruckabfall
  - Obstipation, Durchfall
  - Langsame Herzfrequenz

Neurologische Nebenwirkungen von Thalidomid and Bortezomib

<table>
<thead>
<tr>
<th></th>
<th>Thalidomide¹ ²</th>
<th>Bortezomib³ ⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>extremities: “glove and stocking”</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>symmetrical</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Sensory symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>paraesthesia</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>numbness</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>hyperaesthesia</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>neuropathic pain</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>proprioceptive failure</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Motor symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>decreased muscle strength</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Autonomic symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypotension, impotence, bradycardia</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Anatomic damage caused by thalidomide and bortezomib

<table>
<thead>
<tr>
<th>Peripheral nerves</th>
<th>Thalidomide1,2</th>
<th>Bortezomib3,4</th>
</tr>
</thead>
<tbody>
<tr>
<td>axonal involvement</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>small afferent fibres</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>(Aβ, Aδ, C fibres)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwann cells and myelin</td>
<td>occasionally</td>
<td>predominantly</td>
</tr>
<tr>
<td>Dorsal root ganglia</td>
<td>occasionally</td>
<td>occasionally</td>
</tr>
<tr>
<td>Spinal column</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

1. McBride WG, Teratology 1974;10:283-91

Pathogenesis of thalidomide- and bortezomib-induced PNP

- **Major hypotheses**
  - thalidomide¹
    - down-regulation of TNF-α
    - NFκB-mediated inhibition of nerve-growth-factor mediated neuron survival
  - bortezomib²
    - mitochondrial- and ER-mediated dysregulation of Ca²⁺ homeostasis³
    - NFκB-mediated inhibition of nerve-growth-factor mediated neuron survival
    - auto-immune factors and inflammation (cfr. protection by IMiDs?)
    - altered peripheral autonomic tone

- **Predisposing factors⁴**
  - age
  - pre-existing PN (?)
  - previous exposure to neurotoxic antmyeloma agent (?)
  - diabetes, alcoholism

ER = endoplasmic reticulum.
Enstehung sensorischer Neuropathie durch Thalidomide und Bortezomib

<table>
<thead>
<tr>
<th></th>
<th>Thalidomide</th>
<th>Bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-dependent</td>
<td>yes¹,² correlation between total cumulative dose and clinical involvement</td>
<td>yes CREST trial³ (8% vs 15%) maximum at 30 mg/sqm⁴</td>
</tr>
<tr>
<td></td>
<td>(particularly if &gt; 20 g administered)</td>
<td></td>
</tr>
<tr>
<td>Time-dependent</td>
<td>yes slow onset incidence doubles between 6 and 12 months⁵</td>
<td>yes slow or subacute onset maximum around cycle 5 followed by stabilization⁶</td>
</tr>
<tr>
<td>Reversible?</td>
<td>minimally</td>
<td>&quot;~70% have improvement or resolution within 2–3 months⁷,⁸</td>
</tr>
</tbody>
</table>

⁴ Richardson PG, et al. JCO 2006;24:3113-20
⁵ Mileshkin L, et al. JCO 2006;24:4507-14

Diagnose der Polyneuropathie

- **Klinisch**
  - ask the right questions!
    - general: NCI CTC (e.g. neuropathic pain not in neurology section of v.3)
    - specific: Neurotoxicity FACT/Gynecologic Oncology Group
  - Clinical neurological examination!

- **Electrophysiologisch**: nerve conduction studies, electromyography
  - sensory/motor
  - action potentials: sensory nerve action potential, compound motor action potential
  - conduction velocity
  - latency time

- **Bildgebung**: little value

- **Histologie**: only in exceptional circumstances

Kelly JJ. Rev Neurol Dis 2004;1:133-40
Neurotoxizitäts-Bewertung (GOG)

Based on the functional assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity questionnaire

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

Suggestion for treatment recommendation: Delay, reduce, discontinue

Colson et al. Cancer Nurs 2008;31:239-49

Management der Thalidomid und Bortezomib bedingten Neuropathie

<table>
<thead>
<tr>
<th>Severity of PN</th>
<th>Modification of dose and regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>Bortezomib</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Grade 1 with no pain or Grade 2</td>
<td>Monitor Patient carefully</td>
</tr>
<tr>
<td>Grade 2 with pain or Grade 3</td>
<td>Reduce dose of Thalidomide by 50%</td>
</tr>
<tr>
<td></td>
<td>Withhold Thalidomide, consider restart of Thalidomide at lower dose</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

⇒ Supplement possible vitamin B12 and Folate deficiency
Behandlungsmöglichkeiten bei Polyneuropathie

- **Pharmacological treatment**
  - nutritional supplements: glutamine, L-carnitine, α-lipoic acid
  - medication
    - tricyclic antidepressants: amitriptyline, nortriptyline
    - anticonvulsants: gabapentin, pregabalin
    - opioids: oxycodone, morphine, fentanyl
    - cannabinoids: dronabinol
    - serotonin/norepinephrine-reuptake inhibitors (Cymbalta®)
    - nonsteroidal anti-inflammatory drugs

- **Topical treatment**
  - lidocaine patch
  - capsaicin cream,
  - 0.5% menthol in calamine cream

- **Others**
  - high-dose intravenous gammaglobulins
  - physical exercise

Ergebnisse der Therapie mit Lenalidomid/Dexamethason (RD) vs Lenalidomide/Low-Dose Dexamethason (Rd)

<table>
<thead>
<tr>
<th>Toxizität (Grad ≥3)</th>
<th>RD (N=223)</th>
<th>Rd (N=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenie</td>
<td>2.7%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Thrombocytopenie</td>
<td>1.8%</td>
<td>1.4%</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>25.6%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Atrial Fibrillation/Flutter</td>
<td>3.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Infektion/Pneumonie</td>
<td>16.1%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Ermüdung</td>
<td>11.7%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Hyperglykämie</td>
<td>5.8%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Neuropathie</td>
<td>0.4%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wirkung</th>
<th>RD</th>
<th>Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Jähriger Überlebenszeit</td>
<td>88%</td>
<td>96%</td>
</tr>
<tr>
<td>2-Jähriger Überlebenszeit</td>
<td>75%</td>
<td>87%</td>
</tr>
<tr>
<td>OS in Pts&lt;65 (1 Jahr)</td>
<td>92%</td>
<td>97%</td>
</tr>
<tr>
<td>OS in Pts&gt;65 (1 Jahr)</td>
<td>83%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Deaths: 42 vs 16

Thrombosen und Überleben bei Patienten mit multiplem Myelom (Thal-Dex vs. Dex)

<table>
<thead>
<tr>
<th>Adverse events with any treatment attribution</th>
<th>N = 207</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic event ≥ grade 3</td>
<td>36</td>
</tr>
<tr>
<td>DVT</td>
<td>27</td>
</tr>
<tr>
<td>MI</td>
<td>3</td>
</tr>
<tr>
<td>Stroke</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-related adverse event</th>
<th>n = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>24</td>
</tr>
</tbody>
</table>

Adapted from Kumar S, et al. Blood. 2007;110 [abstract 2734]

Vergleich zwischen Enoxaparin, Aspirin und Warfarin bei Patienten mit MM

<table>
<thead>
<tr>
<th>Thalidomide-containing cohorts (VTD, TD, VMPT)</th>
<th>(n = 347)</th>
</tr>
</thead>
</table>

ASA
Aspirin 100 mg/day

WAR
Warfarin 1.25 mg/day

LMWH
Enoxaparin 40 mg/day

VMP
No prophylaxis

Palumbo et al. Abstract IMWS 200
Häufigkeit einer Thromboembolie unter Aspirin, Warfarin und Enoxaparin

By Prophylaxis

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Enoxaprin</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
</tr>
</tbody>
</table>

By Regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prophylaxis</td>
<td></td>
</tr>
<tr>
<td>VTD</td>
<td></td>
</tr>
<tr>
<td>TD</td>
<td></td>
</tr>
<tr>
<td>VMPT</td>
<td></td>
</tr>
</tbody>
</table>

Behandlung der Knochenmarksuppression

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Anemia</th>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide/Dexamethasone</td>
<td>16%</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>Lenalidomide/Dexamethasone</td>
<td>8%</td>
<td>21%</td>
<td>10%</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>12%</td>
<td>14%</td>
<td>32%</td>
</tr>
</tbody>
</table>

- Myelosuppression management
  - Growth factor therapy
  - Dose reduction as appropriate
- Anemia management
  - Erythropoietins
  - Transfusions
- Thrombocytopenia management
  - Platelet transfusions

Adapted from NLB Consensus Recommendations. CJON June 2008
Knochenmarkfunktion im Laufe langfristiger Behandlung mit Lenalidomid- Dexamethason

Empfehlungen für das Management von Neutropenie unter Lenalidomid + Dexamethason

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*For each subsequent drop and return to a neutrophil count of at least 0.5 × 10⁹/l, the lenalidomide dose should be resumed at the next lower dose.*
Durchfall - Häufige Ursachen

- Neuropathy
- Infections
  - Bacteria (Clostridium, E. Coli, rarely Shigella, Salmonella, Campylobacter and others)
  - Bacterial toxins
  - Viruses (Noro-, Rota-, CMV-Virus)
  - Protozoa (Lamblia)
- Antibiotic associated colitis
- Chemotherapy induced mucositis
- Amyloidosis of GI tract
- Impairment of existing inflammatory bowel diseases

*>=3 stools, >75% water content, ca 10 liter per day reabsorbed

Durchfall – diagnostische Möglichkeiten sollten ausgeschöpft werden

- Clostridium colitis
- Other bacterial infections
- Viral infections
- Motility disorder
- Amyloidosis

Rota-, Norwalck-, Adeno-, CMV-, EBV-, Entero-Virus
Durchfall - Behandlung

- Clarification of the cause and - if possible - causal treatment
- Compensation of fluid loss
  - Oral substitution (per liter 3.5g NaCl, 1.5g KCl, 2.5g sodium bicarbonate (baking soda), 20 g glucose)
- Symptomatic
  - Loperamid (Immodium®, Enterobene®)
  - Diphenoxylate + Atropin (Lomotil®)
  - Budesonid (Entocort®)
  - Somatostatin (Sandostatin LAR®, Somatuline®)
  - Probiotika (Omnibiotic 10®, Omniflora®)
  - Intravenous hydration

Verstopfung

Slow transit constipation
Medicamentous causes
  - Thalidomide, Opioids, Cytostatic drugs, Antipsychotic drugs, Muscle relaxants, Sleeping pills, Aluminum sulfate, Iron products, Diuretics, Antihypertensiva, Antiparkinson drugs, Anticonvulsants, Anticholinergica
Lack of fluids
Lack of exercise
Dysfunction of the pelvic floor
Briden
Hypothyreodism
Verstopfung - Behandlung

Discontinue drugs that induce constipation, fluid supply, exercise, fibers

Increase of feces volume with osmotic laxatives: lactulose, magnesium sulfate

Enhancement of motility, secretion: Senna compounds, Bisacodyl

Expansion: Movicol®, flax seed

Rectal aids for defecation: Clysmol

Enhancement of motility: Cholinesterase inhibitors (Ubretil®, Prostigmin®)

Opioid antagonist: Naltrexon (Relistor®)

Mechanic removal /clearing

Nebenwirkungen mit verschiedenen Behandlungsprotokollen

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Peripher-neuropathy grades 3-4 (%)</th>
<th>DVT/embolism grades 3-4 (%)</th>
<th>Neutropenia grades 3-4 (%)</th>
<th>Thrombocytopenia grades 3-4 (%)</th>
<th>Infection grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant candidates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thal/Dex</td>
<td>3.4</td>
<td>11.5</td>
<td>3.4</td>
<td>ND</td>
<td>7.3</td>
</tr>
<tr>
<td>ASCT-T</td>
<td>27</td>
<td>30</td>
<td>94</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Rev/Dex</td>
<td>0</td>
<td>3</td>
<td>12</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>BPD</td>
<td>4</td>
<td>9</td>
<td>19</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>Bort/Dex</td>
<td>6</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
<td>9</td>
</tr>
<tr>
<td>PAG</td>
<td>16</td>
<td>4</td>
<td>8.1</td>
<td>13.5</td>
<td>10.8</td>
</tr>
</tbody>
</table>

| Non-transplant candidates |
| MPT       | 8                                 | 9                           | 16                        | 3                               | 10                       |
| MPT       | 6                                 | 12                          | 48                        | 14                              | 13                       |
| MPR       | 0                                 | 4.8                         | 52                        | 23                              | 9.5                      |
| MPV       | 17                                | 0                           | 43                        | 51                              | 16                       |

Palumbo-Rajkumar, Leukemia 2009
Prophylaxe von Infektionen

- **Vaccinations**
  - Hemophilus, Menigoccoci, Pneumococci
  - Influenza, Herpes zoster (Zostavax*)
- **Antiviral prophylaxis**
  - Aciclovir, famvir, valciclovir
- **Antibacterial prophylaxis**
  - Levofoxacin, Trimethoprim/sulfamethaxol
- **Antifungal**
  - Fluconazol

Der Erfolg der antibakteriellen Prophylaxe ist klar etabliert

- Chinolones
- Co-Trimoxazol*

*Reduktion der Rate bakterieller Infektionen: 2.43 pro Patienten-Jahr für Kontrollgruppe und 0.29 für Patienten unter Bactrim Prophylaxe (P=0.001)

**Reduktion der Mortalität HR: 0.58, alle Ursachen HR: 0.66

Zusammenfassung

- Prophylaxe und Behandlung von Nebenwirkungen der Myelomtherapie stellt eine bedeutende Maßnahme dar
- Befolgung der Empfehlungen stellt einen Maßstab für die Betreuungsqualität dar
- Führt zu einer Reduktion der Symptome
- Führt zur Verbesserung der Lebensqualität
- Reduziert die Mortalität

Conclusions

- PN is a clinically frequent and important symptom in myeloma patients
- PN can develop as a result of
  - the disease
  - the treatment
  - cytostatics: vincristine, cisplatin
  - thalidomide
  - bortezomib
  - lenalidomide
- the pathogenesis of thalidomide- and bortezomib-induced PN is poorly understood
- PN has a serious impact on the QoL of MM patients
- the diagnosis relies predominantly on clinical awareness
- rapid and appropriate dose modification or interruption is more important than pharmacological intervention
VTE management recommendations for Len + Dex in relapsed/refractory MM

Screening
• No baseline coagulation studies nor screening recommended
• If symptomatic - sonography for VTE diagnosis recommended

VTE prophylaxis
• Patients with risk factors: 4–6 months prophylaxis
  ➢ Low dose aspirin (81–100 mg) or prophylactic dose of LMWH
  ➢ Low-dose warfarin not recommended (risk severe haemorrhage)

VTE treatment
• Continue with Len + Dex or re-treat after stabilization dependent on severity of VTE
  ➢ switch patients on aspirin prophylaxis to LMWH
  ➢ switch patients on LMWH prophylaxis to therapeutic doses (6 months therapeutic dose LMWH after which prophylaxis can be re-started)


Dose modification for bortezomib induced PNP

<table>
<thead>
<tr>
<th>Neuropathy</th>
<th>Action to be taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>no action</td>
</tr>
<tr>
<td>Grade 2, or grade 1 with pain</td>
<td>reduce bortezomib to 1.0 mg/m²</td>
</tr>
<tr>
<td>Grade 3, or grade 2 with pain</td>
<td>withhold bortezomib until toxicity resolves then reinitiate at 0.7 mg/m² and administer once per week</td>
</tr>
<tr>
<td>Grade 4</td>
<td>discontinue bortezomib</td>
</tr>
</tbody>
</table>

Janssen-Cilag. Bortezomib SmPC
Dose modification for thalidomide induced PNP

<table>
<thead>
<tr>
<th>Neuropathy</th>
<th>Action to be taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Monitor patient with clinical examination (or reduce the dose by 50% if symptoms worsen). However dose reduction is not necessarily followed by improvement of symptoms.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>reduce the dose and continue to monitor the patient</td>
</tr>
<tr>
<td></td>
<td>- if no improvement or worsening: discontinue treatment</td>
</tr>
<tr>
<td></td>
<td>- if the neuropathy resolves to grade 1 or better, treatment may be restarted if risk:benefit ratio is favourable</td>
</tr>
<tr>
<td>Grade 3</td>
<td>discontinue treatment</td>
</tr>
<tr>
<td>Grade 4</td>
<td>permanent discontinuation</td>
</tr>
</tbody>
</table>

Celgene. Thalidomide SmPC

Diarrhoea - Pathophysiology

- Motility disorder
  - Neuropathy, irritable bowel syndrome, postoperative

- Secretorice diarrhea
  - Bacterial toxins, VIP (Vasoactive Intestinal Peptide) compensation of dehydration

- Osmotic diarrhea
  - Insufficient resorption caused by mucosa damage

- Chologenic diarrhea
  - Dysfunction of permeability caused by gall bladder, colon cancer, colitis