Understanding and Dealing With Disease-related and Treatment-related Complications in Multiple Myeloma

Mohammad Omaira, MD
West Michigan Cancer Center
January 30, 2015

PRACTICE-CHANGING DEVELOPMENTS FOR PRIMARY CARE PROVIDERS
Disclosures

- I have no financial relationships to disclose
- I will not discuss off label use and/or investigational use in my presentation
Objectives

- Identify common disease-related complications
- Identify treatment-related complications
- Prevention
- Management
Introduction

- Multiple myeloma (MM) is an incurable malignancy characterized by neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin and results in extensive bone destruction, anemia, renal impairment and immune dysfunction.
Clinical Presentation

- Anemia – 73 %
- Bone pain – 58 %
- Elevated creatinine – 48 %
- Fatigue/generalized weakness – 32 %
- Hypercalcemia – 28 %
- Weight loss – 24 %
- Paresthesias – 5 %
Myeloma-related complications

- Anemia: 73%
- Lytic bone lesions: 66%
- Bone pain: 58%
- Renal insufficiency: 30%
- Hypercalcemia: 13%
Disease-related complications

- **Anemia**
  - A normocytic, normochromic anemia (hemoglobin \( \leq 12 \text{ g/dL} \)) is present in 73% at diagnosis and in 97% at some time during the course of the disease
    - bone marrow replacement
    - kidney damage
    - dilution in the case of a large M-protein
  - Anemia commonly results in complaints of fatigue
Anemia - Treatment

- Red blood cell transfusion
- Induction chemotherapy
- Erythropoiesis-stimulating agents (ESAs)

Disease-related complications

- **Skeletal lesions & Bone pain**
  
  Bone pain, particularly in the back or chest, and less often in the extremities, is present at the time of diagnosis in approximately 60 % of patients.
  
  The pain is usually induced by movement.
  
  The patient's height may be reduced by several inches because of vertebral collapse.
  
  Plasmacytomomas of the ribs occur and can present either as expanding costal lesions or soft tissue masses.
Management of Skeletal lesions & Bone pain

- **Prevention of skeletal events:**
  - Bisphosphonate therapy

- **Treatment of fractures:**
  - Stabilization with an intramedullary rod
  - Kyphoplasty or vertebroplasty

- **Pain control**

- **Radiation:** Up to 40% of patients with myeloma will require radiation to control disease at some point in their disease course.
Bisphosphonate Therapy in MM

A

HR 0.87 (95% CI 0.77–0.99)  
p = 0.04

Survival (%)

Time (years)

Zoledronic acid  
Clodronic acid

Number at risk

Zoledronic acid  981  806  675  418  222  79  3
Clodronic acid  979  776  642  399  208  69  0

B

HR 0.64 (95% CI 0.47–0.86)  
p = 0.0044

Survival (%)

Time (months)

981  972  958  949  944  935  927  920  910
979  965  952  937  924  913  898  883  871

Bisphosphonate Therapy in MM

**Bone Disease**

![Graph showing survival data for Bone Disease with CLO and ZOL treatments.](image)

* Censored
* $P = .0107$
* HR = 0.82 (95% CI = 0.70, 0.95)

**No Bone Disease**

![Graph showing survival data for No Bone Disease with CLO and ZOL treatments.](image)

* Censored
* $P = .4690$
* HR = 1.10 (95% CI = 0.86, 1.40)

Morgan G. Blood 2012
Bisphosphonate treatment-related complications

- Gastrointestinal events
- Inflammatory reaction on injection site
- Acute systemic reaction: flu-like symptoms
- Hypocalcemia and hypophosphatemia
- Acute and chronic renal failure
- Avascular osteonecrosis of the jaw (ONJ).
Disease-related complications

- **Renal disease**
  - The serum creatinine concentration is increased in almost one-half of patients at diagnosis (and is >2 mg/dL in approximately 20%), may be the presenting manifestation of MM
    - Light chain cast nephropathy (myeloma kidney)
    - Hypercalcemia
    - Light chain (AL) amyloidosis
    - Light chain deposition disease
    - Drug-induced renal damage
Renal Insufficiency - Management

- Avoidance of nephrotoxins
- Maintenance of hydration
- Dose adjustment for renal insufficiency (lenalidomide, zoledronic acid)
- The choice of initial induction therapy (VCD and VTD)
Disease-related complications

- **Hypercalcemia**

  Hypercalcemia is found in 28% of one series of patients with MM at the time of diagnosis.

  The ionized calcium should be measured if the patient has a high serum calcium level but no symptoms of hypercalcemia.
Management of Hypercalcemia

- Hydration, preferably with isotonic saline, plus either dexamethasone as part of myeloma therapy or prednisone (1 mg/kg per day) is effective in most cases of mild hypercalcemia (eg, serum calcium <12 mg/dL).
- In moderate to severe hypercalcemia (eg, serum calcium >14 mg/dL), treatment includes hydration, corticosteroids, and a bisphosphonate such as zoledronic acid or pamidronate.
- Calcitonin is used if rapid reduction of calcium levels is needed or if patients are refractory to bisphosphonates alone.
Disease-related complications

- **Infection**
- **Immune dysfunction**
  - impaired lymphocyte function
  - suppression of normal plasma cell function
  - hypogammaglobulinemia.
  - chemotherapy induced neutropenia
- **Physical factors**: hypoventilation secondary to pathologic fractures and pain involving the rib cage and spine.
- **Streptococcus pneumoniae** and gram-negative organisms are the most frequent pathogens.
Infection – Prevention and Treatment

- Influenza vaccines and a single pneumococcal vaccine at the time of diagnosis
- All patients receiving bortezomib or carfilzomib, we administer antiviral prophylaxis because of the increased risk of herpes zoster
- Prophylactic antibiotics is controversial
- Infection should be treated promptly with empiric antibiotics covering encapsulated bacteria and gram negative microorganisms
Disease-related complications

- **Neurologic disease**
  - **Radiculopathy**, usually in the thoracic or lumbosacral area, is the most common neurologic complication of MM

- **Cord compression**

- **Peripheral neuropathy**: is uncommon in MM at the time of initial diagnosis and, when present, is usually due to amyloidosis.

- **CNS involvement**: Intracranial plasmacytomas are rare and almost always represent extensions of myelomatous lesions of the skull
<table>
<thead>
<tr>
<th>Treatment Agents in MM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytotoxic drugs</strong></td>
</tr>
<tr>
<td>▸ Melphalan</td>
</tr>
<tr>
<td>▸ Cytoxan</td>
</tr>
<tr>
<td>▸ Bendamustine</td>
</tr>
<tr>
<td>▸ Doxorubicin</td>
</tr>
<tr>
<td>▸ Vincristine</td>
</tr>
<tr>
<td>▸ Etoposide</td>
</tr>
<tr>
<td>▸ Cisplatin</td>
</tr>
<tr>
<td><strong>Immunmodulators</strong></td>
</tr>
<tr>
<td>▸ Thalidomide</td>
</tr>
<tr>
<td>▸ Lenalidomide</td>
</tr>
<tr>
<td>▸ Pomalidomide</td>
</tr>
<tr>
<td>▸ Dexamethasone</td>
</tr>
<tr>
<td>▸ Prednisone</td>
</tr>
<tr>
<td><strong>Proteasome Inhibs</strong></td>
</tr>
<tr>
<td>▸ Bortezomib</td>
</tr>
<tr>
<td>▸ Carfilzomib</td>
</tr>
</tbody>
</table>
Molecular Structures

**Thalidomide**
100-200 mg/d
- Neuropathy
- Constipation
- Sedation
- DVT

**Lenalidomide**
15-25 mg/d
- Myelosuppression
- Skin rash
- DVT

**Pomalidomide**
1-4 mg/d

Structurally similar, but functionally different both qualitatively and quantitatively.
## Proteasome Inhibitor Comparison

<table>
<thead>
<tr>
<th>Biochemical mechanism and selectivity</th>
<th>Carfilzomib</th>
<th>Bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irreversible</strong></td>
<td>(keto-epoxide tetrapeptide)</td>
<td>Slowly reversible</td>
</tr>
<tr>
<td></td>
<td>(boronic acid dipeptide)</td>
<td></td>
</tr>
<tr>
<td><strong>Highly selective for chymotrypsin-like active site within the proteasome</strong></td>
<td></td>
<td>Inhibits both chymotrypsin-like and caspase-like activities of the proteasome</td>
</tr>
<tr>
<td><strong>Highly selective for proteasome</strong></td>
<td>N-terminal threonine active sites</td>
<td>Cross reactivity with serine proteases</td>
</tr>
</tbody>
</table>

### IC$_{50}$s (nM)

<table>
<thead>
<tr>
<th></th>
<th>Carfilzomib</th>
<th>Bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chymotrypsin-like</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Caspase-like</td>
<td>2400</td>
<td>74</td>
</tr>
<tr>
<td>Trypsin-like</td>
<td>3600</td>
<td>4200</td>
</tr>
</tbody>
</table>

* Three distinct N-terminal threonine protease active sites

Stewart, ASCO 2007
Regimens in Newly Diagnosed MM

**Boulelets**
- TD/Td
- RD/Rd
- VD/Vd

**Triplets**
- MPT
- VMP
- VCD (CyBorD)/VCd
- VTD/VTd
- VRD/VRd
- VDT-PACE
## NCCN GUIDELINES

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Therapy for Transplant Candidates</strong> (Assess for response after 2 cycles)</td>
<td>• Carfilzomib&lt;sup&gt;7&lt;/sup&gt;/lenalidomide&lt;sup&gt;4&lt;/sup&gt;/dexamethasone</td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone (category 2B)</td>
</tr>
<tr>
<td></td>
<td>• Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)</td>
</tr>
<tr>
<td></td>
<td>• Thalidomide/dexamethasone (category 2B)</td>
</tr>
<tr>
<td></td>
<td>• Bortezomib/dexamethasone</td>
</tr>
<tr>
<td></td>
<td>• Lenalidomide/low-dose dexamethasone (category 1)&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Melphalan/prednisone/bortezomib (MPB) (category 1)</td>
</tr>
<tr>
<td></td>
<td>• Melphalan/prednisone/lenalidomide (MPL) (category 1)</td>
</tr>
<tr>
<td></td>
<td>• Melphalan/prednisone/thalidomide (MPT) (category 1)</td>
</tr>
<tr>
<td><strong>Primary Therapy for Non-Transplant Candidates</strong> (Assess for response after 2 cycles)</td>
<td>• Dexamethasone (category 2B)</td>
</tr>
<tr>
<td></td>
<td>• Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)</td>
</tr>
<tr>
<td></td>
<td>• Melphalan/prednisone (MP)</td>
</tr>
<tr>
<td></td>
<td>• Thalidomide/dexamethasone (category 2B)</td>
</tr>
<tr>
<td></td>
<td>• Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)</td>
</tr>
<tr>
<td><strong>Maintenance Therapy</strong></td>
<td>• Bortezomib + prednisone (category 2B)</td>
</tr>
<tr>
<td></td>
<td>• Bortezomib + thalidomide (category 2B)</td>
</tr>
<tr>
<td></td>
<td>• Interferon (category 2B)</td>
</tr>
<tr>
<td></td>
<td>• Steroids (category 2B)</td>
</tr>
<tr>
<td></td>
<td>• Thalidomide + prednisone (category 2B)</td>
</tr>
<tr>
<td></td>
<td>• Bortezomib</td>
</tr>
<tr>
<td></td>
<td>• Lenalidomide&lt;sup&gt;5&lt;/sup&gt; (category 1)</td>
</tr>
<tr>
<td></td>
<td>• Thalidomide (category 1)</td>
</tr>
</tbody>
</table>

NCCN 2014
<table>
<thead>
<tr>
<th>Therapy for Previously Treated Multiple Myeloma</th>
<th>Preferred Regimens</th>
<th>Other Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Repeat primary induction therapy (if relapse at &gt;6 mo)</td>
<td>• Bendamustine</td>
</tr>
<tr>
<td></td>
<td>• Bortezomib (category 1)</td>
<td>• Bortezomib/vorinostat</td>
</tr>
<tr>
<td></td>
<td>• Bortezomib/dexamethasone</td>
<td>• Lenalidomide/bendamustine/dexamethasone</td>
</tr>
<tr>
<td></td>
<td>• Bortezomib/lenalidomide/dexamethasone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bortezomib/liposomal doxorubicin (category 1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bortezomib/thalidomide/dexamethasone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Carfilzomib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cyclophosphamide/bortezomib/dexamethasone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cyclophosphamide/lenalidomide/dexamethasone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)</td>
<td>(category 1)</td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclo-</td>
<td>• Pomalidomide/dexamethasone</td>
</tr>
<tr>
<td></td>
<td>phosphamide/etoposide (DT-PACE) ± bortezomib (VTD-</td>
<td>• Thalidomide/dexamethasone</td>
</tr>
<tr>
<td></td>
<td>PACE)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High-dose cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Lenalidomide/dexamethasone (category 1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pomalidomide/dexamethasone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Thalidomide/dexamethasone</td>
<td></td>
</tr>
</tbody>
</table>
**Hematologic adverse events**

- **Thrombocytopenia**
  - Generally not related to the disease itself, except in case of very aggressive disease.
  - It is a quite common side effect in patients treated with bortezomib, carfilzomib, lenalidomide and alkylating agents, while it is rare in patients treated with thalidomide alone or plus steroids.

- When grade 4 thrombocytopenia (platelet count \( \leq 25,000/\text{mm}^3 \)) occurs, treatment should be interrupted and then restarted when the thrombocytopenia resolves to at least grade 2 (platelet count \( \geq 50,000/\text{mm}^3 \)).
Hematologic adverse events

- **Neutropenia**
  - Likely not related to myeloma. It is a common AE of both lenalidomide and alkylating agents, less frequent with bortezomib.
  - In patients considered at high risk of neutropenia on the basis of age, medical history, disease characteristics and the expected myelotoxicity of the treatment regimen, prophylaxis with G-CSF is recommended.
Non-hematologic adverse events

- **Peripheral neuropathy**
  - Rarely a complication of myeloma; if present, it is more commonly related to amyloidosis
  - More likely to be related to bortezomib and thalidomide therapy
  - Thalidomide causes mainly sensory neuropathy, while with bortezomib, both sensory and painful neuropathy

- **Pomalidomide**: rare
- **Carfilzomib**: less common and less severe
Peripheral neuropathy - Management

- Neuropathy is cumulative and dose-dependent

- There are currently no effective medications able to relieve neuropathic symptoms.

- Antidepressants: duloxetine
- Tricyclic antidepressants: nortriptyline
- Anticonvulsants: gabapentin
- Opiods
Bortezomib

Lower risk of grade 3 or higher neuropathy with once-weekly dosing of VMP
13% (twice-weekly-VISTA) vs 7% (once-weekly)
Bortezomib

Lower risk of grade 3 or higher neuropathy with once-weekly dosing of VMP or VMPT
16% (twice-weekly; n=134) vs 3% (once-weekly; n=369)

Palumbo A et al. JCO 2010;28:5101-5109
©2010 by American Society of Clinical Oncology
Non-hematologic adverse events

- **Venous thromboembolism**
  - Incidence of VTE varies from 3 to 10%.
  - Thalidomide and lenalidomide alone do not increase the incidence of VTE, but it substantially increases when dexamethasone or chemotherapy

- Pomalidomide + low-dose dexamethasone: Clinical trials have routinely included thromboprophylaxis with ASA
Venous Thromboembolism

Cumulative risk of DVT among 2374 MGUS cases (solid line), 6192 patients with multiple myeloma (short dashed line), and 4,187,631 persons without a diagnosis of MGUS/multiple myeloma (long dashed line).

Blood. 2008;112(9):3582.
Thalidomidae and VTE

Table 2  Venous thromboembolism incidence in trials of thalidomide or lenalidomide without thromboprophylaxis

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Newly diagnosed patients</th>
<th>Relapsed/refractory patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VTE incidence (%)</td>
<td>References</td>
</tr>
<tr>
<td>Thalidomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>3–4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30,31</td>
</tr>
<tr>
<td>Plus dexamethasone</td>
<td>14–26</td>
<td>24,35,36</td>
</tr>
<tr>
<td>Plus melphalan</td>
<td>10–20</td>
<td>25,26,39</td>
</tr>
<tr>
<td>Plus doxorubicin</td>
<td>10–27</td>
<td>41–43</td>
</tr>
<tr>
<td>Plus cyclophosphamide</td>
<td>3&lt;sup&gt;c&lt;/sup&gt;–11</td>
<td>45,46</td>
</tr>
<tr>
<td>Plus multiagent chemotherapies</td>
<td>16–34</td>
<td>51,52</td>
</tr>
</tbody>
</table>

Table 5  Rate of venous thromboembolism (per 100 patient cycles) in patients with newly diagnosed multiple myeloma treated with thalidomide-based regimens

<table>
<thead>
<tr>
<th></th>
<th>No prophylaxis</th>
<th>Any prophylaxis</th>
<th>ASA</th>
<th>Warfarin 1–1.25 mg per day</th>
<th>Prophylactic LMWH</th>
<th>Therapeutic doses of anticoagulation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide without dexamethasone (95% CI)</td>
<td>1.3 (0.4–2.7)</td>
<td>2.6 (2.1–3.2)</td>
<td>2.3 (0.9–7.9)</td>
<td>2.8 (2.0–3.9)</td>
<td>2.1 (1.1–3.6)</td>
<td>1.6 (0.2–4.1)</td>
</tr>
<tr>
<td>(n = 380)</td>
<td>(n = 993)</td>
<td>(n = 80)</td>
<td>(n = 387)</td>
<td>(n = 446)</td>
<td>(n = 80)</td>
<td></td>
</tr>
<tr>
<td>Thalidomide + dexamethasone (95% CI)</td>
<td>4.1 (2.8–5.9)</td>
<td>2.6 (2.1–3.2)</td>
<td>2.3 (0.9–7.9)</td>
<td>2.8 (2.0–3.9)</td>
<td>2.1 (1.1–3.6)</td>
<td>1.6 (0.2–4.1)</td>
</tr>
<tr>
<td>(n = 628)</td>
<td>(n = 993)</td>
<td>(n = 80)</td>
<td>(n = 387)</td>
<td>(n = 446)</td>
<td>(n = 80)</td>
<td></td>
</tr>
</tbody>
</table>

*Therapeutic doses of anticoagulation: (i) warfarin with target INR between 2.0 and 3.0 or (ii) therapeutic doses of low-molecular-weight heparin. CI, confidence intervals; LMWH, low-molecular-weight heparin; n, total number of patients.
### Lenalidomide and VTE

#### Table 8 Rate of venous thromboembolism (per 100 patient-months) in patients with previously treated multiple myeloma managed with lenalidomide-based regimens in combination with dexamethasone

<table>
<thead>
<tr>
<th></th>
<th>No prophylaxis</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide + dexamethasone (95% CI)</td>
<td>0.7 (0.4–0.9)</td>
<td>(n = 361)</td>
</tr>
<tr>
<td>Lenalidomide + dexamethasone + other chemotherapy agents including doxorubicin (95% CI)</td>
<td>0.6 (0.01–2.1)</td>
<td>(n = 131)</td>
</tr>
</tbody>
</table>

CI, confidence intervals; n, total number of patients.

#### Table 7 Rate of venous thromboembolism (per 100 patient-cycles) in patients with newly diagnosed multiple myeloma treated with lenalidomide-based regimens in combination with dexamethasone

<table>
<thead>
<tr>
<th></th>
<th>No prophylaxis</th>
<th>Any prophylaxis</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide + dexamethasone (95% CI)</td>
<td>0.8 (0.07–2.0)</td>
<td>0.7 (0.5–1.1)</td>
<td>0.9 (0.5–1.5)</td>
</tr>
<tr>
<td>(n = 278)</td>
<td>(n = 349)</td>
<td>(n = 172)</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence intervals; n, total number of patients.
Venous Thromboembolism Prophylaxis

- At present, there are no data on what is the best thromboprophylaxis

- ASA
- LMWH
- Warfarin

Risk stratification
- Body mass index $\geq 30$ kg/m$^2$
- ● Previous VTE
- ● Central venous catheter or pacemaker
- ● Cardiac disease (e.g., symptomatic CAD, CHF, or history of stent placement/CABG)
- ● Chronic kidney disease
- ● Diabetes mellitus
- ● Acute infection
- ● Immobilization
- ● Use of erythropoietin
- ● Inherited thrombophilia
Non-hematologic adverse events

- **Gastrointestinal adverse events**
  - **Thalidomide**: constipation
  - **Lenalidomide**: diarrhea.
  - **Bortezomib-based regimens**: constipation and diarrhea
  - **Carfilzomib**: nausea and diarrhea

- **Management**
  - Symptomatic management
  - Dose reduction
Non-hematologic adverse events

- **Dermatologic adverse events**
  
  - Both thalidomide and lenalidomide can cause dermatologic toxicity, most frequently
    - Rash
    - Dry skin
    - Mouth and atrophic lesions.
  
  - Bortezomib-based regimens: rare
<table>
<thead>
<tr>
<th>Drug</th>
<th>Common AEs &gt;15%</th>
<th>Occasional AEs</th>
<th>Rare AEs &lt;5%</th>
</tr>
</thead>
</table>
| **Thalidomide** | Venous thromboembolism  
Peripheral neuropathy  
Neutropenia  
Thrombocytopenia  
Sedation/Fatigue  
Constipation | Skin rash  
Cardiac events  
Seizure (rare) |                                                                            |
| **Lenalidomide** | Neutropenia  
Infection  
Thrombocytopenia  
Gastrointestinal  
Fatigue | Skin rash  
Neuropathy  
Toxic epidermal necrosis  
Steven-Johnson Sx |                                                                            |
| **Pomalidomide** | Neutropenia  
Gastrointestinal  
Pneumonia  
Fatigue  
Skin rash | Peripheral neuropathy  
VTE |                                                                            |
| **Bortezomib** | Neutropenia  
Thrombocytopenia  
Peripheral neuropathy  
Gastrointestinal  
Pneumonia  
Cardiac events  
Fatigue  
Rash  
VTE | Herpes Zoster reactivation  
Pulmonary HTN |                                                                            |
| **Carfilzomib** | Fatigue  
Nausea  
Neutropenia/Lymphopenia  
Thrombocytopenia | Peripheral neuropathy  
Pneumonia  
Hypertension  
CHF |                                                                            |