Management of early complications of chemotherapy and targeted therapies

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Emesis and Management
Emesis

- Nausea and vomiting -- devastating side effects of antineoplastic agents
- Uncontrolled emesis affect quality of life and impair compliance with treatment
- About 70-80% patients experience emesis & 10-44% have anticipatory emesis
Emesis
Categories of Emesis

- Acute - <1 day p chemo
- Delayed - 1-7 days p chemo
- Breakthrough - despite pre-treatment
- Anticipatory - prior to chemo
- Refractory - continued emesis
Emesis

The potential for Chemotherapy induced Nausea and Vomiting (CINV) is influenced by

• Emetogenic potential of antineoplastic agents
• Patient related factors
## Emetogenic potential of cytostatics

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Risk of emesis w/o antiemesis</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>&gt; 90 %</td>
<td>Cisplatin, Dacarbazine, Nitrogen mustard</td>
</tr>
<tr>
<td>moderate</td>
<td>30-90%</td>
<td>Carboplatin, anthracyclines, ifosfamide, oxaliplatin, irinotecan</td>
</tr>
<tr>
<td>low</td>
<td>10-30%</td>
<td>Etoposide, gemcitabine, 5- FU, mitoxantrone, capecitabine, docetaxel, paclitaxel,</td>
</tr>
<tr>
<td>minimal</td>
<td>&lt; 10%</td>
<td>Bleomycin, vinblastine, hormones</td>
</tr>
</tbody>
</table>
## Patient Related Risk Factors

<table>
<thead>
<tr>
<th>Major factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Age &lt; 50 years</td>
</tr>
<tr>
<td>History of low prior chronic alcohol intake</td>
</tr>
<tr>
<td>History of previous chemotherapy-induced emesis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of motion sickness</td>
</tr>
<tr>
<td>Emesis during past pregnancy</td>
</tr>
<tr>
<td>Adverse Event</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>mechanism of action</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>5-HT₃-receptor</td>
</tr>
<tr>
<td>multiple</td>
</tr>
<tr>
<td>Neurokinin-1-receptor</td>
</tr>
<tr>
<td>Dopamin-D₂-Receptor</td>
</tr>
<tr>
<td>GABA-Chlorid-channel</td>
</tr>
<tr>
<td>Dopamin-D₂-Receptor</td>
</tr>
<tr>
<td>Not known</td>
</tr>
<tr>
<td>Muscarin-Cholin-Rec.</td>
</tr>
</tbody>
</table>
## Optimal dosage of setrons

<table>
<thead>
<tr>
<th>Setron</th>
<th>Dosage</th>
<th>Ondansetron</th>
<th>8 mg</th>
<th>16-24 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granisetron</td>
<td>1 mg</td>
<td>2 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tropisetron</td>
<td>5 mg</td>
<td>5 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolasetron</td>
<td>100 mg</td>
<td>100-200mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palonosetron</td>
<td>0.25 mg</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

given 30 min. before chemotherapy.

Roila F. Ann Oncol 2006;17(1):20-8  
Kris MG. J Clin Oncol 2006;24(18):2932-47
Acute emesis following chemotherapy of high risk emetogenic potential

- The combination of a 5-HT3 antagonist plus a corticosteroid represents the standard of care
- Addition of aprepitant to standard antiemetic therapy improves control
- Palonosetron
Acute emesis following chemotherapy

• Should be given prophylactic antiemetics
• Patients should maintain oral fluid intake
• If vomiting persists may require parenteral antiemetics and/or admission for rehydration.
ANTIEMETICS FOR THE PREVENTION OF DELAYED EMESIS INDUCED BY HIGH RISK EMETOGENIC CHEMOTHERAPY

DELAYED EMESIS FOLLOWING CISPLATIN CHEMOTHERAPY

• All patients receiving cisplatin at doses $\geq 50$ mg/m² should receive antiemetic prophylaxis for delayed emesis
ANTIEMETICS FOR THE PREVENTION OF DELAYED EMESIS INDUCED BY HIGH RISK EMETOGENIC CHEMOTHERAPY

- Palonosetron
- Aprepitant
- Cannabinoids Improves Outcomes
Antiemetic guidelines
- MASCC, ASCO-

<table>
<thead>
<tr>
<th>Emetogenic potential</th>
<th>acute emesis (&lt; 24h)</th>
<th>⇒</th>
<th>delayed emesis (&gt; 24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High &gt; 90%</td>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt;-RA +</td>
<td>⇒</td>
<td>dexamethasone (day 2-4) +</td>
</tr>
<tr>
<td></td>
<td>dexamethasone +</td>
<td>⇒</td>
<td>aprepitant (day 2-3)</td>
</tr>
<tr>
<td></td>
<td>aprepitant</td>
<td>⇒</td>
<td></td>
</tr>
<tr>
<td>Moderate 30% - 90%</td>
<td>1. 5-HT&lt;sub&gt;3&lt;/sub&gt;-RA +</td>
<td>⇒</td>
<td>1. aprepeitnant (day 2-3)</td>
</tr>
<tr>
<td></td>
<td>dexamethasone+</td>
<td></td>
<td>(+ dexamethasone)</td>
</tr>
<tr>
<td></td>
<td>aprepeitnant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. 5-HT&lt;sub&gt;3&lt;/sub&gt;-RA +</td>
<td>⇒</td>
<td>2. dexamethasone or alternative</td>
</tr>
<tr>
<td></td>
<td>dexamethasone</td>
<td></td>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt;-RA</td>
</tr>
</tbody>
</table>
## Antiemetic guidelines

- **MASCC, ASCO**

<table>
<thead>
<tr>
<th>Emetogenic potential</th>
<th>acute emesis (&lt; 24h)</th>
<th>⇒</th>
<th>delayed emesis (&gt; 24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low 10% - 30%</td>
<td>dexamethasone mono</td>
<td>⇒</td>
<td>No therapy</td>
</tr>
<tr>
<td>Minimal &lt; 10%</td>
<td>No therapy</td>
<td>⇒</td>
<td>No therapy</td>
</tr>
</tbody>
</table>

Roila F. Ann Oncol 2006;17(1):20-8
Kris MG. J Clin Oncol 2006;24(18):2932-47
The probable most potent antiemetic therapy in PEB

<table>
<thead>
<tr>
<th>antiemetics</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5-HT(_3)-antagonist or (Palonosetron 0.25 mg i.v.)</td>
<td>X</td>
</tr>
<tr>
<td>Dexamethasone 8 mg i.v.</td>
<td>X</td>
</tr>
<tr>
<td>Aprepitant p.o.</td>
<td>125</td>
</tr>
</tbody>
</table>

ASCO 2007
Managing Mucositis
Mucositis

- Stomatitis
- Cheliosis
- Glossitis
- Oral ulceration
- Oesophagitis
- Superadded infection (e.g. Candida)
- Reduced diatery intake
Mucositis

- Mtx
- 5 FU
- Anthracyclines
- Bleomycin
- Vinblastin
- Actinomycin D
- Etoposide
- ARA-C
# Mucositis

World Health Organization Grading of Mucositis/Stomatitis

<table>
<thead>
<tr>
<th>Grade</th>
<th>(Symptoms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>I</td>
<td>Painless ulcers, erythema, or mild soreness</td>
</tr>
<tr>
<td>II</td>
<td>Painful erythema, edema, or ulcers, but can eat</td>
</tr>
<tr>
<td>III</td>
<td>Painful erythema, edema, or ulcers, but cannot eat</td>
</tr>
<tr>
<td>IV</td>
<td>Requires parental or enteral support</td>
</tr>
<tr>
<td>V</td>
<td>Death</td>
</tr>
</tbody>
</table>
Mucositis Managing

Treatment is supportive and aimed at symptom control

• Maintain oral hygiene (e.g. mouthwash)
• Adequate fluid intake
• Treat candida
• Use analgesia to reduce pain
Impact of Palifermin on Mucositis-Related Transplantation

• Phase 3 trial of palifermin, recombinant human keratinocyte growth factor

• Previous reports from this trial demonstrated that palifermin reduces incidence, severity, and duration of mucositis [1]

• Data reported at ASH examined impact of palifermin on hospital transplantation costs [2]

Diarrhea

National Cancer Institute Common Toxicity Criteria for Diarrhoea

Grade 0: Increase of less than 4 stools/day over baseline
Grade 1: Increase of 4-6 stools/day over baseline
Grade 2: Increase of greater than 7 stools/day over baseline, incontinence
Grade 3: Life-threatening consequences including extremely low blood pressure as a result of severe dehydration
Grade 4: Death
FL plus Irinotecan

• Neutropenia, alopecia, fatigue, vomiting and
• Diarrhea: any grade was seen in 50 to 88 % (severe in 9 to 31 %)

predisposing factors
older age,
low performance status
prior pelvic radiation
whites
inherit genetic polymorphisms such as the UGT1A1*28 allele
Irinotecan-related diarrhea

- Early-onset: (cholinergic excess) mean duration of symptoms is 30 minutes it is well controlled by atropine.
- Late diarrhea: (6.-11. days) less common with the every three week schedule loperamide treatment
Diarrhea

• Other diarrhea-related drugs: 5 FU, MTX, 6 MP, ARA-C, Actinomycin D, Anthracyclines

MANAGEMENT

• Oral or intravenous hydration
• Loperamide, diphenoxylate
• Octreotide
• Codein phosphate
• Dose reduction of MTX or 5 FU may require, if severe diarrhea
# Grading of Constipation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema</td>
</tr>
<tr>
<td>2</td>
<td>Persistent symptoms with regular use of laxatives or enemas indicated</td>
</tr>
<tr>
<td>3</td>
<td>Symptoms interfering with ADL; obstipation with manual evacuation indicated</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences (eg, obstruction, toxic megacolon)</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>
Constipation

- Vinca-alkoloids (25-33%), thalidomide (35-59%), opiates

MANAGING

- Advise patients on nutritional adjustments, eg, increasing fiber and fluid intake
- Patients should increase their level physical activity, if possible
- Stool softeners (lactulose), mild purgatives (senna) magnesium salts
- Patients should notify physician if no bowel movement in 3 days
Risk of Chemotherapy-Induced Neutropenia
Incidence of Chemotherapy-Induced Neutropenia in Cancer Patients

- Myelosuppression a major dose-limiting toxic effect of cancer chemotherapy

- Prospective, nationwide study of 2302 cancer patients
  - Patients enrolled before beginning chemotherapy
  - Mean 3 cycles completed

- Neutropenic outcomes
  - Neutropenia: ANC nadir < $10^9$/L
  - Severe neutropenia (SN): ANC nadir < $0.5 \times 10^9$/L
  - Febrile neutropenia (FN): fever or infection, ANC nadir < $10^9$/L
  - Severe FN: fever or infection, ANC nadir of $0.5 \times 10^9$/L

Incidence of Chemotherapy-Induced Neutropenia in Cancer Patients

- First chemotherapy cycle associated with higher rate of neutropenia than 3 subsequent cycles

Febril Neutropenia

- Check full blood count
- Look for source of infection
- Blood and urine cultures, chest radiograph
- Start broad-spectrum antibiotics and G-CSF
- Add other drugs for specific clinical indication
- Line removal for non-resolving line infections.
Bleeding

• As many as 10%, result from thrombocytopenia,

• abnormalities in plasma levels of the coagulation factors (e.g. L-Asparaginase),
Bleeding

• 11% incidence of platelet nadirs < 20,000 µlt (n:1,192)

• 75 / 718 (10%) patients had an episode of serious hemorrhage (no fatal bleeding occurred at plt > 10,000mlt)

• The risk of hemorrhage was associated with the rapidity of the drop in platelet count and the presence of active infection
Bleeding

• not at significantly increased risk of spontaneous hemorrhage until the platelet count is below 10,000 µlt, if no other risk factors are present

• Patients with active hemorrhage may require transfusion of platelets, (plt 20,000 - 50,000 µlt), since platelet dysfunction (e.g. Mithramycin) may be present
Management of Thrombocytopenia

• Platelet transfusions
• Dose adjustment

• Avoid medications that may increase risk of bleeding (eg, aspirin)
• Immediately report bruising or uncontrolled bleeding
Thrombocytopenia
Anemia Treatment Options

- Transfusion of 1 U is estimated to increase hemoglobin level by average of 1 g/dL
- Risks: transfusion-related reactions, congestive heart failure, bacterial/viral contamination and infection, and iron overload
Anemia Treatment Options

Erythropoetin

- Major benefit is decrease in transfusion requirements for chemotherapy patients
- Risks: higher risk of mortality and tumor progression, thromboembolism, hypertension and seizures, and pure RBC aplasia
- Indicated only for patients receiving palliative chemotherapy
- Should not be started if hemoglobin > 10 g/dL
Renal Toxicity

- Cisplatin
- Carboplatin
- MTX
- Cyclophosphamide / Ifosfamide
- Streptozocin

- Dose modification is needed in renal failure
Hematuria

- Hematuria can be due to therapy-induced hemorrhagic cystitis, commonly from cyclophosphamide and ifosfamide
- Acrolein has cytotoxic effects on the bladder mucosa
- use of the urinary acrolein neutralizer 2-mercaptoethane sulfonate (Mesna)
Tumor Lysis Syndrome

• acute hyperuricemia, urate nephropathy, and acute renal failure,
• hyperkalemia,
• hyperphosphatemia
• hypocalcemia,
• cardiac arrhythmias, and
• sudden death
Tumor Lysis Syndrome

- The best management of TLS is prevention
- allopurinol, 600 to 900 mg per day orally, should be initiated 48 hours before therapy
- recombinant urate oxidase (uricozyme)
- hydration and diuresis of at least 3,000 mL per day,
  with urinary pH of at least 7.0 (unclear and controversial)
- mannitol or high-dose furosemide
- dialysis
Tumor Lysis Syndrome

Acute life-threatening hyperkalemia
- Kayexalate,
- intravenous glucose and insulin,
- dialysis

Hyperphosphatemia:
- aluminum hydroxide antacids,
- dialysis
Pulmonary toxicity

• can be debilitating and life threatening
• Rapid recognition of this problem and its management are critical if morbidity is to be limited.
• Bleomycin has long been known to cause interstitial pneumonitis (BIP)
• The incidence of BIP is 10%, with a fatality rate of between 1 and 2%
Pulmonary toxicity

- **Gemcitabine** is associated with an uncommon but serious interstitial pneumonitis and which develops rapidly within 72 hours.
- The incidence has been estimated at between 0.02% and 0.06%
- **Irinotecan** is a topoisomerase 1 inhibitor, which has been linked to pulmonary toxicity.
- Progressive deterioration followed by death was typical, with no response to corticosteroids.
Adult Respiratory Distress Syndrome

ARDS has been reported as a complication of

• all-trans retinoic acid therapy in patients with promyelocytic leukemia (retinoic acid syndrome),
• gemcitabine therapy

• Treatment is primarily supportive
Hepatotoxicity

- Elevated hepatic enzymes: nitrosoureas, ARA-C
- Cholestasis: 6 MP, Azathioprine
- Necrosis: Mithramycin
- Vena occlusive disease (VOD): High-dose alkylating agents (e.g. busulfan, nitrosoureas), 6 MP, 6 TG, ARA-C, azathiaprine
Ocular Toxicity

• Visual disturbance:
  Blurring: 5 FU
  Transient cortical blindness: Cisplatin, carboplatin

• Conjunctivitis, dry eyes: 5 FU, Mtx

• Excess lacrimation: 5FU, Mtx, Doxorubicin

• Cataracts: Busulphan
Hypersensitivity Reaction (HSR) ANAPHYLAXIS

• TYPE I HSR: urticaria, pruritis, angioedema, dyspnoea, bronchospasm and hypotension L-asp, paclitaxel, etoposide, cisplatin, procarbasine, Rare: anthracyclines, cyclophosphamide, Mtx

• TYPE III HSR: fever, eosinophilia, pneumonitis
Cutaneous Toxicity
Rashes

- Aminoglutethamide
- Procarbazine
- Chlorambucil
- Allopurinol
Photosensitivity

- 5 FU
- Vinblastin
- DTIC
- Thiotepa
- Mtx
Chemotherapy Extravasation
Irritant drugs

- It may produce pain, phlebitis, or local hypersensitivity reactions
- Irritant = an agent capable of causing pain at the injection site or along the vein without resulting prolonged inflammation or tissue damage
Irritant Drugs

- Busulfan
- Carmustine (BCNU)
- 2-Chlorodeoxyadenosine (2-CdA)
- Dacarbazine (DTIC)
- Docetaxel
- Etoposide (VP-16)
- G-CSF and GM-CSF
- Mithramycin
- Pentostatin
- Streptozocin
- Teniposide (VM-26)
Vesicant Drugs

- Vesicant = a cancer chemotherapeutic agent capable of forming a blister and/or causing tissue destruction;
- overall incidence, 0.1 - 6.6 %
- necrotic ulcers persist for many weeks or months after the initial extravasation
- resulting in loss of function, contractures, nerve damage, and causalgia
Vesicant Chemotherapeutic Agents

- Actinomycin
- Daunorubicin
- Doxorubicin
- Epirubicin
- Idarubicin
- Mechlorethamine
- Mitomycin
- Paclitaxel
- Vinblastine, Vincristine, Vinorelbine
Management of Chemotherapy Extravasation

- Drug administration is stopped immediately
- cross-clamped intravenous line and needle should then be aspirated and removed
- to cool the site with ice packs immediately and to continue cooling, for 24 hours,
- rest and elevation of the limb
- Consultation with a plastic surgeon (large-volume extravasation, or if progressive pain, swelling, or ulceration are evident at 48 hours)
Chemotherapy Extravasation

Treatments for anthracycline extravasations

- local injections of corticosteroids,
- GM-CSF, sodium bicarbonate,
- sodium thiosulfate, or
- topical dimethyl sulfoxide (DMSO),
- Dexrazoxane
- with or without α-tocopherol

are all clinically unproven
Chemotherapy Extravasation

• use of corticosteroid injections or cold compresses may exacerbate tissue injury with

• vinca alkaloids and etoposide.
CHEMOTHERAPY EXTRAVASATION

1. CROSS CLAMP IV
2. ASPIRATE LINE
3. REMOVE IV
4. VESICANT DRUG
   - NO → DOCUMENT AND OBSERVE
   - YES → DOCUMENT
5. CLASS OF DRUG
   - ANTITUMOR ANTI-BIOTIC
   - COLD COMPRESS, LIMB ELEVATION
   - VINCA/TAXANE
   - WARM COMPRESS, INJECT 150–900 U HYALURONIDASE
   - NITROGEN MUSTARD
   - 4–6 mL INJECTION OF 0.17 M SODIUM THIOSULFATE
6. SURGICAL CONSULT
   - YES
7. ULCERATION
   - NO → OBSERVE
ALOPESIA
ALOPECIA

FREQUENT and SEVERE
• Anthracyclines
• Paclitaxel
• Ifosfamide
• Cyclophosphamide (IV)
• Vindesine
• Bleomycine
• Actinomycin

MODERATE, DOSE DEPENDENT
• 5 FU
• Mitoxantrone
• Etoposide
• Methotrexate
• Vinblastine
• Vincristine
• Carmustine
• Hydroxyurea
SKİN and NAIŁ CHANGES

DOCETAXEL
Nail Changes

- Beau’s line:
- Pigmentasyon: anthracyclines, bleomycin, 5 FU, hydroxyurea, alkylating agents
- Oncolyses: 5 FU, doxorubicin, bleomycin
- Brittle nails: 5 FU, Hydroxyurea
Hand and Foot Syndrome

- Capecitabine, 5FU, continuous-infusion doxorubicin, doxorubicin liposomal (18%)
  high-dose Interleukin-2
- Palmar-plantar erythrodysesthesia
- Redness, tenderness, and possibly peeling of the palms and soles that prevents normal activity.
- Usually mild, has started as early as 2 weeks after start of treatment.
- May require reductions in the dose of the medication.
Hand-Food Syndrome

Grade 1
Numbness, dysesthesia or paresthesia, tingling, painless swelling or erythema, and/or discomfort of hands or feet not disrupting normal activities

Grade 2
Painful erythema and swelling of hands or feet and/or discomfort affecting ADLs

Grade 3
Moist desquamation, ulceration, blistering or severe pain of hands or feet, or severe discomfort preventing work or performance of ADLs
Hand and Foot Syndrome

• Modifying some of your normal daily activities to reduce friction and heat exposure to your hands and feet
• Avoid long exposure of hands and feet to hot water
• Avoid increased pressure on the soles of the feet or palms of hands
• Dishwashing gloves should not be worn
• Cold may provide temporary relief for pain and tenderness
Radiation Recall

- Actinomycin D
- Bleomycin
- Doxorubicin
- Epirubicin

Intensive steroid therapy
Biologic Therapies

- Hypotension,
- Tachyarrhythmias,
- Angina,
- Myocardial infarction,
- Congestive heart failure

have been reported as complications of treatment with interleukin-2 (IL-2), various interferons, and monoclonal antibodies.
Thalidomide: Adverse Events

• Common adverse events
  – Constipation: 55%
  – Fatigue: 79%
  – Somnolence
  – Sensory neuropathy: 54%
  – Rash: 30%

• Key grade ≥ 3 toxicities
  – Deep vein thrombosis: 4-15% (depending on use with steroids)
  – Peripheral neuropathy
  – Weakness
Lenalidomide: Adverse Events

• Common adverse events
  – Constipation: 39%
  – Fatigue: 38%
  – Diarrhea: 29%
  – Neutropenia: 28%

• Key grade $\geq 3$ toxicities
  – Deep vein thrombosis: 7%
  – Neutropenia: 21%
  – Thrombocytopenia: 10%
## Adverse Events of Endocrine Therapy (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>TAM (%)</th>
<th>AI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes</td>
<td>40.9</td>
<td>35.7</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>10.2</td>
<td>5.4</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>13.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Venous thromboembolic</td>
<td>4.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Joint symptoms</td>
<td>29.4</td>
<td>35.6</td>
</tr>
<tr>
<td>Bone Fractures</td>
<td>7.7</td>
<td>11</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>5.1</td>
<td>1.3</td>
</tr>
</tbody>
</table>
Bisphosphonates (BP)

- BP are beneficial in terms of skeletal morbidity and to reduce bone pain including opioid resistant pain
- Zoledronic acid should be considered in all patients with bone metastases from solid tumours
- BP should be considered as soon as bone metastases are diagnosed even if they are asymptomatic

Intravenous Bisphosphonates: Adverse Effects

Generally well tolerated but be aware of

- Renal dysfunction
- Osteonecrosis of the jaw, and
- Acute phase reaction
Bisphosphonates (BP)

• **Flu-like symptoms: ~ 20%**
  – Arthralgia, myalgia, nausea, low-grade fever, bone pain
  – Typically self-limiting

• **Hypocalcemia: reported cases**
  – All patients should receive calcium and vitamin D supplementation

• **Acute renal toxicity: rare (Zoledronic Acid)**
  – Monitor serum creatinine
  – Drug not indicated in patients with creatinine clearance < 30 mL/min

• **Osteonecrosis of the jaw: 0.6% to 20.0% (Zoledronic Acid)**
  - Remove and treat all dental infections prior to treatment
  – Maintain good oral hygiene and routine dental care
  – Avoid elective dental procedures and oral surgeries

Management of early complications of targeted therapies
EGFR TKI

- Gefitinib: Rash or acne, diarrhea, elevated liver enzymes
- Erlotinib: Rash, diarrhea

Advers Events
Rash
Diarrhea
Febrile neutropenia
Infusion-released reactions
Trastuzumab

- Infusion-associated symptoms, including fever and chills, primarily with first dose
- Increased incidence of cardiac dysfunction, particularly when administered with anthracycline-based therapy
- Serious adverse events infrequent

FL plus Irinotecan-Bevacizumab

- Neutropenia 29
- Venous thromboembolic events 18 + 1 ex
- Diarrhea 12
- Fatigue 10
- Vomiting 7
- Deep vein thrombosis 7
- Pulmonary embolism 7 + 1 ex
- Nausea 6
- Febrile neutropenia 6 + 1 ex
- Hypertension 5
- Bleeding 4 (53%, mostly epistaxis)
- Arterial thromboembolic events 4 + 1 ex
- Proteinuria 2
- Gastrointestinal perforation 2 + 1 ex
- Wound-healing complications <1
- Congestive heart failure 1
- Fistula/abscess 1 + 1 ex

Sobrero A, Oncology 2009;77:113–119
Imatinib

- Fluid retention, superficial edema, facial edema, periorbital edema, weight gain
- Neutropenia (myelosupression 10% to 30% in CML)
- Tumor lysis syndrome (rare)
- Nausea, vomiting, diarrhea,
- Skin rashes
- Myalgia, muscle cramps, fatigue, headache,
- Serious but uncommon side effects: (1% to 2%) hepatic, renal or cardiopulmonary dysfunction

- Management with dose reductions or treatment interruptions.
sunitinib
### Sunitinib Adverse Events Grade 3-4,

<table>
<thead>
<tr>
<th>Condition</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
</tr>
<tr>
<td>Hand-foot Syndrome</td>
<td>6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6</td>
</tr>
<tr>
<td>Yellow skin, rash, skin discolouration, hypothyroidism, epistaxis, cardiac failure</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

*(Lancet Oncol 2009; 10: 757–63)  (Motzer JR. JCO June 1, 2009)*
Sorafenib

- Diarrhea (39%)
- Hand-foot syndrome (21%)
- Anorexia (14%)
- Alopecia (14%)

Hypophosphatemia (11%), Hypertension (2%), Abdominal pain (2%), Thrombocytopenia (4%),


<table>
<thead>
<tr>
<th>Drug-Related Grade 3/4 Adverse Events Occurring in &gt; 5% of Patients, %</th>
<th>Sorafenib (n = 297)</th>
<th>Placebo (n = 302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>8</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>
LAPATİNİB

- Rash
- Diarrhea
- Anorexia
- Anemia
- Asthenia
# Bortezomib: Common Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events, n (%) (N = 331)</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>190 (57)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>117 (35)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>190 (57)</td>
<td>24 (7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>140 (42)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>140 (42)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>115 (35)</td>
<td>97 (20)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>62 (19)</td>
<td>48 (15)</td>
</tr>
<tr>
<td>Anemia</td>
<td>87 (26)</td>
<td>33 (10)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>120 (36)</td>
<td>26 (8)</td>
</tr>
</tbody>
</table>

Rituximab

• Mild-to-moderate infusion-related reactions (eg, chills, fever, malaise)
  • usually with the first infusion; fatalities have been reported within 24 hours of infusion;

• Generally self limited, improve with slowing of the infussion, monitor closely and discontinue with grades 3 or 4 infusion reactions

• Persistent hypogammaglobulinemia, B cell depletion
• serious viral infection after rituximab treatment (HBV, HCV, CMV, VZV)
• Progressive multifocal leukoencephalopathy
• Renal toxicity, Tumor lysis syndrome

• Use with caution in patients with pre-existing cardiovascular disease or prior cardiopulmonary events.(arrhythrias and angina pectoris)
Thank you for your attention

Zeki Üstüner M.D.