Minimizing Chemotherapy-Induced Side Effects and Complications Associated with Cancer

Dr. Dapo Ajibola Amosu
VP, Zyrix Health Systems
This document contains proprietary and confidential information. All information contained herein are provided in reliance upon its consent not to be used or disclosed except in the context of its business dealings with Zyrix Health. The recipient of this document agrees to inform present and future employees who view or have access to its content of its confidential nature. The recipient agrees to instruct each employee that they must not disclose any information concerning this document to others. The recipient also agrees not duplicate or distribute or permit others to duplicate or distribute any material contained herein without Zyrix Health's express written consent. Zyrix Health retains all title, ownership and intellectual property rights to the material and trademarks contained herein, including all supporting documentation, files, marketing material, and multimedia. BY ACCEPTANCE OF THIS DOCUMENT, THE RECIPIENT AGREES TO BE BOUND BY THE AFOREMENTIONED STATEMENT.
Introduction

• Cancer and chemotherapy complications result in:
  – Treatment delays
  – Reduction in treatment intensity
  – Compromised treatment outcomes
  – Excess healthcare costs/expenses
  – Emotional distress
  – Morbidity and mortality
Complications of Chemotherapy

• Short term
  – Febrile neutropenia; nausea/vomiting; diarrhea; infusion-related reactions; TLS
  – Mucositis; anemia; extravasation; cardiotoxicity; hypersensitivity reactions; etc

• Long term
  – Cardiac disease; MDS
  – Secondary malignancies (leukemia, etc)
  – Neuropathy; arthropathy
Cardiotoxicity of Anticancer Agents

- Anthracyclines and anthraquinone
  - Doxorubicin, epirubicin, mitoxantrone
  - Epirubicin is less cardiotoxic than Doxo
    - Dexrazoxane is recommended for cumulative dose of doxorubicin ≥300 mg/m² in metastatic disease

- ErbB2 inhibitor: Trastuzumab

- VEGF signaling pathway inhibitors:
  - Sunitinib and Sorafenib

- Reported clinical cardiac complications are:
  - Arrhythmias
  - Myocardial necrosis resulting in dilated cardiomyopathy
  - Vasoocclusion or vasospasm
    - Resulting in angina or myocardial infarction

Zyrix Health Systems
Proposed Mechanisms for Cardiotoxicity Due to Anthracyclines and ErbB Inhibitors.

- Anthracyclines
  - Increased Oxidative Stress (Iron, Top2β, Rac1)
  - Progenitor Cell Inhibition
  - Titin Proteolysis
  - Neuregulin/ErbB Inhibition
  - Apoptosis

- Potential Cardioprotective Therapies:
  - Anthracyclines: Dexrazoxane, Statins, β-blockers, ACE-inhibitors, Exercise, Neuregulin
  - Trastuzumab: β-blockers, ACE-inhibitors, Exercise

Virginia Shalkey Hahn et al. J Am Heart Assoc 2014;3:e000665
## Management of Chemo-Induced Cardiotoxicity

<table>
<thead>
<tr>
<th>Class of Cancer Therapy</th>
<th>Potential Cardioprotective Therapies</th>
<th>Hypothesized Biologic Mechanisms of Action</th>
<th>Available Evidence</th>
</tr>
</thead>
</table>
| Anthracyclines          | Doxorubicine                        | - Decreased ROS formation via prevention of anthracycline–iron complex formation  
- Reduced anthracycline-induced DNA damage via inhibition of Top2–DNA cleavage complexes | In vitro and in vivo animal studies  
Randomized clinical trials  
Meta-analyses |
| HMG-CoA reductase inhibitors | Bevacizumab                         | - Reduced cell death and Top2β-mediated DNA damage via Rac1 inhibition | In vitro and in vivo animal studies  
Retrospective clinical studies and small randomized clinical trial |
| β-Blockers              |                                    | - Increased prosurvival signaling via recruitment of β-arrestin and transactivation of EGFR  
- Mitigation of oxidative stress  
- Enhanced lusitropy | Small randomized clinical trials, including combination ACE inhibitor and β-blocker therapy |
| ACE inhibitors          |                                    | - Attenuated oxidative stress and interstitial fibrosis  
- Improved intracellular calcium handling  
- Improved cardiomyocyte metabolism  
- Improved mitochondrial function | Randomized clinical trials, including combination ACE-inhibitor and β-blocker therapy |
| Exercise training       |                                    | - Decreased ROS formation  
- Reduced pro-apoptotic signaling  
- Improved calcium handling  
- Improved myocardial energetics via augmented AMPK activity | In vivo animal studies |
| Bivalent neuregulin     |                                    | - Biased ErbB signaling | In vitro and in vivo animal studies from single laboratory |
| Trastuzumab             | ACE inhibitors                      | - Decreased angiotensin-induced blockade of NRG-1/Erbb pathway | Retrospective clinical studies (in combination with β-blockers) |
|                         | β-Blockers                          | - Increased prosurvival signaling via recruitment of β-arrestin and transactivation of EGFR | Retrospective clinical studies (one in combination with ACE inhibitors) |
|                         | Exercise                            | - Enhanced NRG-1/Erbb signaling  
- Increased myocardial Akt  
- Inhibition of TGF-β signaling | Small, single group study with failure to demonstrate an attenuation of trastuzumab-induced LV dilation |
| Sunitinib               | Thalidomide                         | - Improved pericyte function via PDGFR signaling | In vivo animal studies from single laboratory |
|                         | AMPK activators                     | - Restoration of favorable myocardial energetics | In vitro and in vivo data |
EGFR Inhibitor–Related Dermatologic Toxicities

- EGFR is expressed in the epidermis, follicle, sebaceous, eccrine glands, etc
- EGFR inhibition leads to negative effects on skin
  - Apoptosis, inflammation, atrophy, telangiectasias, ↓ photoprotection
- Consequences of dermatologic conditions
  - Psychosocial impact
  - Financial burden
  - Physical health
  - Anticancer treatment disruption


Zyrix Health Systems
EGFR Inhibitor–Related Dermatologic Toxicities

- **Red papulopustules**[1]
  - Pruritus, tenderness in 62%
- **Erlotinib 150 mg QD**[2]
  - All grade: 75%
  - Grade 3: 9%
- **Cetuximab**[3]
  - All grade: 85%
  - Grade 3: 10%
- **Panitumumab**[4]
  - All grade: 90%
  - Grade 3: 16%
- **Lapatinib**[5]
  - All grade: 27%
  - Grade 3: 1%

---

STEPP Study: Preemptive vs Reactive Skin Toxicity Treatment in Metastatic CRC

- Open-label phase II study
- **Prophylactic** skin treatment regimen administered Wks 1-6 (beginning Day 1)
  - Skin moisturizer
  - Sunscreen (PABA free, SPF ≥ 15, UVA/UVB protection)
  - Topical steroid (1% hydrocortisone cream)
  - Doxycycline 100 mg BID
- Per investigator discretion, **reactive** skin treatment administered anytime during wks 1-6
**STEPP: Dermatologic Toxicities**

<table>
<thead>
<tr>
<th>Dermatologic Toxicity</th>
<th>Prophylactic (n = 48)</th>
<th>Reactive (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with grade 2 or higher skin toxicity, n (%)</td>
<td>14 (29)</td>
<td>29 (62)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.3 (0.1 - 0.6)</td>
<td></td>
</tr>
</tbody>
</table>

A 62-year-old man with colorectal cancer is currently undergoing chemotherapy with capecitabine and oxaliplatin. He presents with gradual bilateral development of pain, redness, numbness, and desquamation of his palms (shown).

What is the most likely diagnosis?

a. Stevens-Johnson syndrome
b. Psoriasis
c. Palmar-plantar erythrodysesthesia
d. Toxic shock syndrome
Palmar-plantar erythrodysesthesias, (hand-foot syndrome) is associated with:

- Capecitabine,
- 5-Fluorouracil
- Docetaxel.

Symptoms resolve within 1–2 weeks after discontinuance of the offending chemotherapy agent.

Pyridoxine relieves mild symptoms

Not effective for capecitabine-related cases
• Mortality has diminished but remains significant.
• Mortality rates
  – 5% in people with solid tumors (1% in low-risk) 11% in patients with hematological malignancies.
• Prognosis is worst in people with:
  – Gram-negative bacteremia: mortality rates of 18%
  – Gram-positive bacteremia: mortality rate of 5%
• Elderly people are at a higher risk
Chemo-related Febrile Neutropenia

• Febrile neutropenia (FN):
  – Oral temperature >38.3°C
  – 2 consecutive readings of >38.0°C for 2 hrs
  – Absolute neutrophil count <0.5X10^9/l, or expected to fall below 0.5 X10^9/L

• Empiric treatment
  – Low risk: oral or IV antibiotics
  – High risk: IV broad spectrum antibiotics
Febrile Neutropenia Treatment Algorithm

Fever (temperature ≥38.3°C) + Neutropenia (<500 neutrophils/mm³)

- Low risk
  - Oral: Ciprofloxacin + Amoxicillin-clavulanate (adults only)
  - Monotherapy: Cefepime, Ceftazidime, or Carbapenem

- High risk
  - Iv: Vancomycin not needed
  - Vancomycin needed
    - Two Drugs: Aminoglycoside + Antipseudomonal penicillin, Cefepime, Ceftazidime, or Carbapenem
    - Vancomycin + Cefepime, ceftazidime, or carbapenem ± aminoglycoside
  
Reassess after 3–5 days
Cochrane Review

• Objectives
  – To evaluate the safety and efficacy of adding G-CSF or GM-CSF to antibiotics when treating CIFN

• Participants
  – Individuals undergoing chemotherapy for cancer who experienced neutropenia and fever

• Types of interventions
  – Intervention group: G-CSF or GM-CSF plus antibiotics
  – Control group: antibiotics plus no further treatment or placebo

• Primary outcomes
  – Overall mortality; infection-related mortality

• Secondary outcomes
  – Duration of G4 neutropenia; number hospitalized for > 10 days
Results

• 14 RCTs on the role of CSF in CIFN
• Analysis of 14 trials with 1533 participants
• CSF + antibiotics n=797; antibiotics: n = 756
• Demonstrate the superiority of antibiotics plus CSF
  – In reducing the duration of hospitalization and expediting neutrophil recovery
Implications for Practice

• CSF plus antibiotics did **NOT** improve overall survival
• It reduced the:
  – Time participants spent in hospital
  – Duration of neutropenia
  – Time to recovering from fever
  – Time to withdrawal from antibiotics.
• Patient receiving CSF plus antibiotics:
  – Had a faster neutrophil recovery
  – Similar adverse events compared with antibiotics alone
• Impact of CSF plus antibiotics on infection-related mortality was unclear.
ASCO Key Recommendations

• Use antibacterial and antifungal prophylaxis if neutrophils are expected to remain 100/L for 7 days
• Oral fluoroquinolone is preferred for antibacterial prophylaxis
• Oral triazole for antifungal prophylaxis
• Assess risk using MASCC score or Talcott’s rules
• Oral fluoroquinolone plus amoxicillin/clavulanate is recommended for initial empiric therapy
A 40-year-old man with metastatic colorectal cancer is currently receiving chemotherapy with irinotecan, oxaliplatin, and 5-fluorouracil (5-FU). He reports oral pain and difficulty swallowing. Physical examination of his oral cavity is shown. What is the most likely diagnosis?

a. Oral candidiasis
b. Herpes simplex
c. Mucositis
d. Herpes zoster
Chemotherapy-Induced Oral Mucositis

- This image demonstrates ulcerative oral mucositis.
- 5-FU is associated with oral mucositis
- It involves molecular, cellular, and tissue-based changes
- Genetic susceptibility may play a role.
- Oral mucositis is usually self-limiting
- Resolves approximately 2–4 weeks after completion of chemotherapy

Zyrix Health Systems
Mucositis

- Mucositis is mucosal damage due to cancer therapy
- It occurs in the:
  - Oral cavity, pharyngeal, laryngeal, and esophageal regions
  - Other areas of the gastrointestinal tract
- It can be caused by chemotherapy and/or radiation therapy.
- It occurs in approximately:
  - 20% to 40% of patients receiving conventional chemotherapy,
  - 80% of HSCT patients receiving high-dose chemotherapy
  - All patients receiving head and neck radiation therapy
Chemotherapy-Induced Mucositis

- Chemotherapeutic agents causing mucositis
  - Alkylating agents
    - Busulfan, Cyclophosphamide, thiotepa, procarbazine
  - Anthracyclines
    - Doxorubicin, epirubicin, daunorubicin
  - Antimetabolites
    - 5-FU, methotrexate, hydroxyurea
  - Antitumor agents
    - Actinomycin D, bleomycin, mitomycin
  - Taxanes
    - Paclitaxel
  - Vinca alkaloids
    - Vincristine, vinblastine
Gastrointestinal Mucositis

• Treatment recommendations include:
  – IV amifostine 340 mg/m² for prevention of radiation proctitis.
  – Octreotide 100 µg SQ BID for diarrhea due to high-dose chemotherapy
Approaches to Managing Oral Mucositis

• Prophylaxis
  – 30 min of oral cryotherapy to prevent oral mucositis in patients receiving bolus 5-FU
  – Palifermin (keratinocyte growth factor)

• Benzydamine mouthwash
  – Prevention of oral mucositis in HNC patients receiving LD radiation treatment

• Topical and systemic pain management
  – 2% viscous lidocaine, magic mouthwash preparations; transdermal fentanyl, morphine mouth rinse,
  – Oral rinse containing doxepin
  – Morphine PCA
    • Treatment of pain in HSCT patients
A 65-year-old man with stage IV NSCLC presents with fatigue, rash, and dark urine. He is currently receiving **gemcitabine and carboplatin**. Physical examination reveals conjunctival pallor and a bilateral lower-extremity petechial rash. The patient’s peripheral blood smear is shown.

Pertinent laboratory findings include hemoglobin 8.0 g/dL, platelet count 15 × 10^9/L, creatinine 3.1 mg/dL, lactate dehydrogenase 1,200 U/L (normal: <600 U/L), haptoglobin 15 mg/dL, prothrombin time 12 s (normal: 10-13 s), and activated partial thromboplastin time 30 s (normal: 27-39 s). **What is the most likely diagnosis?**

1. Immune thrombocytopenic purpura
2. Thrombotic thrombocytopenic purpura
3. Sickle cell crisis
4. Disseminated intravascular coagulation
Thrombotic Thrombocytopenic Purpura

• The PBS shown reveals schistocytes (red arrows) and thrombocytopenia.
• The presence of microangiopathic hemolytic anemia, renal impairment, and thrombocytopenia is suggestive of thrombotic thrombocytopenic purpura (TTP).
• Chemotherapy drugs such as gemcitabine and mitomycin have been reported to cause secondary TTP, (caused by decreased levels of the enzyme ADAMTS13).
A 19-year-old woman presents with worsening bilateral hip pain (right worse than left) for the past month. She has acute lymphoblastic leukemia and is currently undergoing maintenance chemotherapy every 3 months with vincristine, prednisone, mercaptopurine, and methotrexate.

What is the most likely cause of the patient's bilateral hip pain?

a. Osteoarthritis of the hip
b. Trochanteric bursitis
c. Avascular necrosis of the femoral head
d. Osteomyelitis
Avascular Necrosis

- **Avascular necrosis (AVN)** of the femoral head is a known complication in patients receiving high-dose steroids as part of their chemotherapy.
- The anterolateral aspect of the femoral head is the most vulnerable site for development of AVN.
- MRI of the hip is the most sensitive means of diagnosing AVN (arrows).
A 55-year-old black man recently diagnosed with AML is currently undergoing induction chemotherapy. One day after he received rasburicase for the prevention of tumor lysis syndrome, his hemoglobin level dropped from 11.1 g/dL to 6.2 g/dL. Lab findings include: lactate dehydrogenase 1,900 U/L (normal <600 U/L), haptoglobin 10 mg/dL, and total bilirubin 3.0 mg/dL.

What is the most likely diagnosis?

- Sickle cell anemia
- Glucose-6-phosphate dehydrogenase deficiency
- Hereditary spherocytosis
- Autoimmune hemolytic anemia
• The PBS shows spherocytes, and bite cells (arrows), which are pathognomonic of G6PD deficiency.
• The disease is inherited as an X-linked disorder,
• Has highest prevalence among Africans, Asians and Mediterraneans
• Exposure of patients with G6PD deficiency to oxidative drugs (rasburicase, dapsone, or sulfonamides) results in rapid hemolysis of the RBCs under stress.
Disease-Related Skeletal Complications

- **Metastatic Breast Cancer**
  - Bone is the most common site of metastasis
  - Affects up to 90% of women with advanced disease
  - Majority of bone metastases from MBC are osteolytic

- **Bisphosphonates**
  - Inhibitors of bone resorption
  - Prevent bone resorption by causing osteoclast apoptosis
  - Pamidronate and zoledronate are potent aminobisphosphonates approved for management of skeletal metastases.
  - These two agents do not eradicate lesions
  - Reduce the proportion of patients experiencing further skeletal-related events by 20%
A 55-year-old woman with stage IV ER+ve breast cancer with bone metastasis presents with left maxillary pain, swelling, and halitosis. She is currently on anastrozole (an aromatase inhibitor) and monthly zoledronic acid for prevention of bone metastasis-related complications. In view of the physical examination finding shown, what is the most likely diagnosis?

- Salivary gland neoplasm
- Osteomyelitis
- Squamous cell carcinoma of the hard palate
- Osteonecrosis of the jaw
Osteonecrosis of the jaw is associated with high-dose bisphosphonate use in patients with cancer.

Bisphosphonates inhibit osteoclasts as well as prevent osteoblast apoptosis, resulting in decreased bone turnover and inhibition of the bone's reparative ability.

Osteonecrosis of the jaw, long-bone fractures, and chronic kidney function impairment are 3 adverse events of "special interest"
• Efficacy of Zoledronic acid Q 12 weeks vs Q month (after 1 year of the standard schedule)
• Randomized 403 women with breast cancer and bone metastases
• Result:
  – Similar skeletal-related event rates (22.0% vs 23.2%)
  – Similar time to first skeletal-related event and bone turnover markers
  – Fewer cases of osteonecrosis of the jaw (2 vs 0)
  – Chronic kidney function impairment (7.9% vs 9.6%)
  – No cases of long-bone fractures (atypical femoral fractures
  – These findings were not statistically significant ($P = .724$)
Chemotherapy-Induced Nausea and Vomiting: Severe (>90%)

- Cisplatin
- Mechlorethamine
- Streptozotocin
- Cyclophosphamide >1500 mg/m²
- Carmustine
- Dacarbazine
Chemotherapy-Induced Nausea and Vomiting: Moderate (30%–90%)

- Oxaliplatin
- Cytarabine >1 gm/m2
- Carboplatin
- Ifosfamide
- Cyclophosphamide <1500 mg/m2
- Doxorubicin

- Daunorubicin
- Epirubicin
- Idarubicin
- Irinotecan
- Azacitididine
- Bendamustine
- Clofarabine
- Alemtuzumab
## Chemotherapy-induced Emesis: MASCC and ESMO Guidelines

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Chemotherapy</th>
<th>Antiemetic guidelines</th>
<th>MASCC Level of Scientific Confidence/Level of Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (&gt;90%)</td>
<td>Cisplatin and other HEC</td>
<td>Day 1: 5-HT&lt;sub&gt;3&lt;/sub&gt; receptor antagonist + DEX + (fos)aprepitant</td>
<td>High/high</td>
</tr>
<tr>
<td></td>
<td>(see Tables 1 and 2)</td>
<td>Days 2–3: DEX + aprepitant</td>
<td>High/Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 4: DEX</td>
<td>High/Moderate</td>
</tr>
<tr>
<td>Moderate (30%–90%)</td>
<td>AC</td>
<td>Day 1: 5-HT&lt;sub&gt;3&lt;/sub&gt; receptor antagonist + DEX + (fos)aprepitant&lt;sup&gt;a&lt;/sup&gt;</td>
<td>High/High</td>
</tr>
<tr>
<td></td>
<td>Non-AC MEC</td>
<td>Days 2–3: aprepitant</td>
<td>Moderate/Moderate</td>
</tr>
<tr>
<td></td>
<td>(see Tables 1 and 2)</td>
<td>Day 1: Palonosetron + DEX</td>
<td>Moderate/Moderate</td>
</tr>
<tr>
<td>Low (10%–30%)</td>
<td>See Tables 1 and 2</td>
<td>Days 2–3: DEX days 2–3</td>
<td>Moderate/Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 1: DEX or 5-HT&lt;sub&gt;3&lt;/sub&gt; or dopamine receptor antagonist</td>
<td>Moderate/Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Days 2–3: no routine prophylaxis</td>
<td>No confidence possible/ Moderate</td>
</tr>
</tbody>
</table>
A 32-year-old man with testicular cancer completed 3 cycles of chemotherapy with bleomycin, etoposide, and cisplatin 3 months ago. He presents with a complaint of exertional dyspnea of recent onset. His chest radiograph is shown. **What is the most likely diagnosis?**

a. Pulmonary edema  
b. Pulmonary fibrosis  
c. Multilobar pneumonia  
d. Pulmonary hemorrhage
This CT scan of the lung shows extensive pulmonary fibrosis, likely induced by bleomycin.

• Bleomycin, busulfan, and methotrexate are known to cause lung toxicity.
• Pulmonary fibrosis should be suspected in patients receiving these drugs and who have corresponding radiologic findings.
A 56-year-old woman presents with a 3-month history of fatigue and exertional dyspnea. She has a history of breast cancer and completed 4 cycles of chemotherapy with doxorubicin and cyclophosphamide 5 years ago. Physical examination is significant for conjunctival pallor. A complete blood count reveals hemoglobin of 7.1 g/dL, mean corpuscular volume of 112 fl, white blood cell count of $2.9 \times 10^9$/L with 33% neutrophils, and a platelet count of $88 \times 10^9$/L. Her peripheral blood smear is shown.

What is the most likely diagnosis?

a. Aplastic anemia
b. Paroxysmal nocturnal hemoglobinuria
c. Myelodysplastic syndrome
d. Vitamin B12 deficiency
Myelodysplastic Syndrome (MDS)

Answer: C.
The PBS reveals a hypolobulated neutrophil, oval macrocytic red blood cells (RBCs), and giant platelets, all of which are commonly seen in patients with myelodysplastic syndrome (MDS).

MDS can occur after treatment for another malignancy with alkylating agent (e.g., cyclophosphamide, busulfan, melphalan).

Latency period for MDS after alkylating agent therapy is 3–7 years.
Questions & Comments