Overview of Biochemotherapy

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• The following material was presented to clinical nurses and nurse practitioners on the pediatric unit at M. D. Anderson Cancer Center in 2006
Introduction

• What is biochemotherapy?
  - Combination of chemotherapy with immunological therapy
• When is biochemotherapy used?
  - Malignant melanoma

Introduction

• Why biochemotherapy?
  - Malignant melanoma can carry a poor prognosis
  - Chemotherapy alone produces a response rate of 10-30% with durable remission in less than 2% of patients
  - Immunotherapy response rates about the same
  - Combination therapy may increase response rates and produce more durable remissions
Biochemotherapy Components

• **Chemotherapy**
  - Dacarbazine 800 mg/m² IV over 1 hour on Day 1
  - Vinblastine 1.5 mg/m² IV push or short infusion on Day 1-4 (give with prehydration for the cisplatin)
  - Cisplatin 20 mg/m² IV over 1 hour on Day 1-4 (after prehydration completes)

• **Immunotherapy or Biotherapy**
  - Aldesleukin (IL-2) 9 million units/m² as a CIVI over 24 hrs Day 1-4 starting after cisplatin (do not stop infusion for chemotherapy)
  - Interferon Alfa 2B (Intron A) 5 million units/m² SQ Day 1-5 (Start with IL-2 or by 2100 on Day 1)
Biochemotherapy Noncomponents

• Steroids (need MD order)
  - You do not want to suppress the immune system since you are giving immunotherapy to activate the patient’s immune system

• Diuretics (need MD order)
  - Fluid balance is very tenuous and must be monitored carefully

Constitutional Side Effects

• Flu-like symptoms
  - Fever, chills, myalgia and malaise
Constitutional Side Effects

- **Characteristics**
  - Fever and chills usually Day 1 (3-6 hrs after first interferon injection)
  - Fever can be high (39-40°C)
  - Fever and chills usually are not as severe on subsequent days
  - Malaise is most marked on Day 5-6 and lasts into 2nd week due to cumulative effects of interferon and interleukin therapy (patients start to feel better by 3rd week)

- **Management**
  - Acetaminophen - may consider giving around the clock starting with first dose of biotherapy. Fever may still occur despite scheduled doses (but will be less severe)
  - Consider NSAID (if platelets are ok) for very high fever (Naproxen given on Day 1 after interferon as one-time dose)
  - Meperidine for rigors
Hematological Effects

• All patients will experience to varying degrees anemia, thrombocytopenia and neutropenia – monitor CBC daily starting on Day 3
• Effects tend to be cumulative
• Thrombocytopenia and leukopenia are common to see by Day 5 and tends to resolve rapidly (due to biotherapy)
  – RN must check platelets on Day 3-5 and act accordingly
• Significant myelosuppression seen in the 2nd or 3rd week after treatment (due to chemotx)

Hematological Effects

• Management
  - Pegfilgrastim 24-72 hrs after therapy x 1 dose to prevent neutropenia (given on Day 7)
  - Darbepoetin x 1 dose to prevent anemia (given on Day 7 if Hgb less than or equal to 11 gm/dL)
Hematological Effects

- Management
  - For severe neutropenia and/or thrombocytopenia, patients may need 25% dose reductions in their dacarbazine and vinblastine during subsequent treatments

Gastrointestinal Toxicities

- Anorexia
- Nausea
- Vomiting
- Constipation
- Diarrhea
- Increased LFTs
Gastrointestinal Toxicities

• Nausea/Vomiting
  - Severe on Day 1 due to dacarbazine
  - Delayed on Day 3-7 due to cisplatin
  - Give 5-HT3 antagonists ATC + Aprepitant Day 1-3
  - Must omit steroids, so suboptimal control
  - Adjunctive meds - Pepcid, Benadryl, Ativan, ABH, Phenergan, Marinol (Reglan should be used with caution because of EPS and diarrhea)
  - If severe, may need to hold week 2 interferon doses (if prescribed) and dose reduce cisplatin by 25% in future treatments

Gastrointestinal Toxicities

• Constipation
  - Usually occurs Day 1-3
  - Secondary to high/frequent doses of 5-HT3 antagonists as well as vinblastine
  - Do not give prophylactic medications or treat because ...
**Gastrointestinal Toxicities**

- **Diarrhea**
  - Usually starts around Day 4 and lasts until Day 8-9
  - Due to biotherapy
  - Evaluate for other causes (e.g. C. diff)
  - Loperamide or Lomotil
  - Tincture of opium if severe

- **Anorexia** (Nutrition consult)
  - Most severe during administration of therapy and lasts up to 1 week after completion
  - Adults can loose 2-3 kg/cycle
  - Consider Megace or Marinol to prevent

- **Increase in LFTs**
  - Treatment modifications are usually not necessary (monitor with daily labs starting Day 5)
Cardiovascular Toxicities

• Common to see hypotension and capillary leak syndrome (IL-2)
  - Due to release of nitric oxide from endothelial cells that produce vasodilation and increased permeability of blood vessels
  - Monitor BP and for s/s of edema every 4 hours

Cardiovascular Toxicities

• Hypotension
  - Discontinue antihypertensives at least 24 hours before starting therapy
  - Usually mild and can be managed with increasing IVF rate or giving fluid boluses of NS (albumin usually not necessary)
  - Moderate (10-40% of patients) may require pressors (low dose dopamine - less than 5 mcg/kg/min) and may need to stop IL-2 infusion
Cardiovascular Toxicities

• Hypotension
  - If severe (not responding to interventions), then transfer to ICU for increased dopamine infusion and phenylephrine
  - Severe not common - you should rule out sepsis

Cardiovascular Toxicities

• Hypotension
  - May need to hold additional doses of medications (not always done at MDACC)
  - Resume biotherapy at 50% dose reductions
  - Doses are not necessarily “made up”
  - If it occurs on 2nd cycle and pressors are needed, biotherapy may need to be completely omitted
Cardiovascular Toxicities

- **Capillary Leak Syndrome**
  - Universal (weigh patient daily)
  - I/O's on every shift
  - Some fluid retention is actually desirable to help with renal perfusion
  - In adults, peripheral edema and weight gain is common and can be 5-10 kg
  - Mannitol has been used to assist with fluid retention

- **Dyspnea**
  - Usually mild and exhibits as bilateral rales (monitor breath sounds and O2 saturations)
  - Upon completion of IL-2 patients have a brisk diuresis and baseline weight usually is achieved by Day 10
  - Diuretics are often unnecessary
Cardiovascular Toxicities

- Rare
  - Cardiac arrhythmias (most commonly atrial fibrillation)
  - Myocardial ischemia
  - Myocarditis
  - CHF

Renal and Electrolyte Disturbances

- Increases in creatinine
- Hypomagnesemia
- Hyponatremia
Renal and Electrolyte Disturbances

- Increases in serum creatinine (Greater than 1.6 mg/dL in adults)
  - You must continually check the serum creatinine
  - Prior to giving Day 3 of cisplatin - RN must check and act accordingly
  - IL-2 (pre-renal and readily reversible)
  - Cisplatin (acute tubular necrosis)

Renal and Electrolyte Disturbances

- Prehydrate each dose of cisplatin
- Maintain good urine output with IVF, fluid boluses and low dose pressors
- Notify MD after every shift for fluid imbalances or decreases in UOP
- Diuretics may be necessary
- May need to hold later doses of cisplatin and IL-2
Renal and Electrolyte Disturbances

- **Hyponatremia**
  - Usually dilutional in nature and often does not require intervention
  - Monitor with daily labs

Renal and Electrolyte Disturbances

- **Hypomagnesemia (cisplatin)**
  - Can lead to muscle weakness and cardiac arrhythmias
  - Can become progressively worse with subsequent cycles and can persist for months after therapy has completed
  - Monitor with daily labs
  - Oral or IV magnesium supplements (but watch if patient has diarrhea)
Infections

• Higher than with chemotherapy alone
  - IL-2 impairs neutrophil function
  - IL-2 associated with skin toxicity
  - Frequent accessing of catheters
• Approximately 2/3 of patients will experience F/N and almost half will have frank bacteremia

Infections

• Common pathogens
  - Coagulase-negative staphylococci
  - *Staphylococcus aureus*
  - Gram-negative bacteria
• If a fever develops after Day 3, many consider this to be infectious in origin
Infections

- Prophylactic G-SCF
- Prophylactic antibiotics?
- Treatment follows similar guidelines for fever/neutropenia
  - Blood cultures
  - Antibiotics
- May need dose reductions by 25% of dacarbazine and vinblastine if neutropenic fever is documented

Cutaneous and Mucosal Toxicities

- All patient will experience diffuse erythema or maculopapular rashes
Cutaneous and Mucosal Toxicities

• Skin rash (IL-2)
  - Mild on Day 1 and worst on Day 5 with resolution by Day 10
  - Do not apply anything to the skin rash
  - May be associated with pruritis that can be severe (treat with hydroxyzine)
  - Dry skin with mild-moderate exfoliation common in weeks 2 and 3 (use skin emollients such as Eucerin lotion, Basis soap, lanolin on lips)

Cutaneous and Mucosal Toxicities

• Oropharyngeal edema (IL-2)
  - Occurs in approximately 20% of patients
  - Subsides by Day 7-9
  - Not caused by infectious agents
  - Supportive care
Cutaneous and Mucosal Toxicities

- Alopecia (Chemo and IL-2)
  - Usually is mild after two cycles and can be more pronounced with more treatment
  - Vitiligo (10-20% of patients)

Endocrine Toxicities

- Hypothyroidism (IL-2)
  - 20-40% of patients
  - May be confused with recurrence of disease because both can have increased LDH and fatigue
  - Monitor thyroid function tests Q 3 months
  - Levothyroxine to maintain TSH levels
Neurological Effects

- Peripheral neuropathy
  - Due to cisplatin and vinblastine
  - Common in patients who receive more than 3 cycles
  - Peak incidence is 1-3 months after therapy has ended
  - Can be severe in approximately 20% of patients
  - Supportive care (Neurontin)

Neurological Effects

- Insomnia
  - Frequent vital signs and forced diuresis
  - May give Ativan, Ambien, Restoril, etc.
- Confusion (IL-2)
  - Common at higher doses but rare with biochemotherapy
  - Fall precautions
- Depression
  - Psychosocial support
  - Antidepressants
Miscellaneous Points

• Patients receiving high doses of IL-2 are more likely to experience hypersensitivity reactions to cisplatin or dacarbazine.

• Patients on IL-2 therapy are more likely to experience adverse reactions to IV contrast.