



Overview of Biochemotherapy

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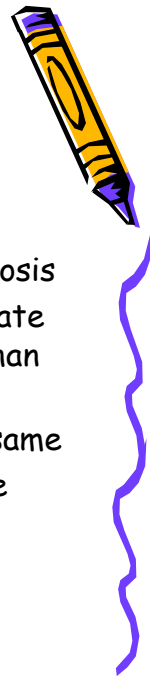
Introduction

- 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)



Biochemotherapy Components

- 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)



Constitutional Side Effects

- 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



Gastrointestinal Toxicities

- Anorexia (Nutrition consult)
 - Most severe during administration of therapy and lasts up to 1 week after completion
 - Adults can lose 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



Cardiovascular Toxicities

- 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

