Didactic Session - Management of Hematologic Toxicities in HCV Therapy

Todd S Wills, MD
USF ETAC, Infectious Disease Specialist

FROM A Guide for Evaluation and Treatment of Hepatitis C in Adults Coinfected with HIV  Mark S. Sulkowski, Laura W. Cheever, David H. Spach
Drug/Toxicity Links

• Anemia – Ribavirin
• Thrombocytopenia – Pegylated Interferon
• Neutropenia – Pegylated Interferon
Management of Treatment Related Anemia

• For Symptomatic Anemia or Hgb <10 g/dL

• STEP 1:
  – Reduce Ribavirin by 200 mg for patient receiving 800-1200 mg/d
  – Reduce Ribavirin dose by 400 mg for patients receiving 1400 mg/d

• STEP 2:
  – Reduce Ribavirin by another 200 mg for patients who have not responded 2 weeks after dose reduction (provided current dose is 800mg/d or greater)
Management of Treatment Related Anemia – Special Situations

• Immediately reduce ribavirin dose to 600 mg/d for the following situations:
  – A sharp decline in hemoglobin in the first 4 weeks of treatment
  – Moderate to severe symptoms of anemia
  – High Cardiovascular Risk

• Dose should not be reduced below 600 mg/d
Management of Treatment Related Anemia – Special Situations

• Ribavirin dose should remain at reduced level if patient is not receiving erythrocyte-stimulating agents

• If the patient is given an erythrocyte-stimulating agent, the ribavirin dose can be slowly increased when Hgb approaches or exceeds 10 g/dL

• If Hgb persist at a level less than 8.5 g/dL despite dose reduction and erythrocyte stimulating factors, ribavirin should be discontinued
Use of Erythrocyte-Stimulating Agents

• **Benefits:**
  
  • Helpful in patients not responding to ribavirin dose reductions
  
  • May minimize the need for ribavirin dose reductions
    – Especially important in patients who do not achieve an RVR
Use of Erythrocyte-Stimulating Agents

• **Risks:**

• Adjuvant therapy has not been shown prospectively to increase likelihood of SVR.

• In patient with malignancy and end-stage renal disease, the agents have been linked to increased risk of:
  – Thrombosis, hypertension, CV events, tumor progression, and rarely red cell aplasia.
Use of Erythrocyte-Stimulating Agents

• Dosing:

• Epoetin alfa – 40,000 IU SC/ week

• Darbepoetin alfa 200 mcg SC every other week

• Goal: 1g/dL or more increase in Hgb in 2 weeks

  – If goal not achieved, change epoetin alfa to 60,000 IU/week, darbepoetin to 300 mcg/ every other week
Use of Erythrocyte-Stimulating Agents

• Outcome goal:
  • Hgb between 10-12 g/dL but not exceeding 12 g/dL
    • Hgb of >13 g/dL resulting from erythrocyte stimulating agents has been linked to increased mortality and cardiovascular complications
  • Some experts will maintain the use of erythrocyte stimulating agents and slowly increase ribavirin dose when Hgb is between 10-12 g/dL
Use of Erythrocyte-Stimulating Agents

• **Failure to Respond:**
  • Evaluate iron, total iron binding capacity, B12, folate and reticulocyte count
  • If Hgb *consistently* declines while taking an erythrocyte-stimulating agent, evaluate for pure red cell aplasia
Management of Thrombocytopenia

• Primary strategy is pegylated interferon dose reduction

• Therapy should be discontinued for platelet count less than 25,000 cell/mm³
Level 1 Peginterferon Dose Reduction - thrombocytopenia

- Platelets <40,000 but >25,000 cells/mm³
- Peginterferon alfa-2a
  - Reduce dose from 180 to 135 mcg
- Peginterferon alfa-2b
  - Reduce dose from 1.5 to 1.0 mcg/kg
- Maintain peginterferon dose at reduced level as subsequent increase will result in another platelet decline
- Monitor platelets every 1-2 weeks until stabilized
Level 2 Peginterferon Dose Reduction - thrombocytopenia

• Further decline in platelets (but still >25,000 cells/mm³)
• Peginterferon alfa-2a
  – Reduce dose from 135 to 90 mcg
• Peginterferon alfa-2b
  – Reduce dose from 1.0 to 0.5 mcg/kg
• Maintain peginterferon dose at reduced level
• Monitor platelets every 1-2 weeks until stabilized
Management of Neutropenia

- Primary strategy is peginterferon dose reduction
- Permanent discontinuation rarely necessary, but temporary discontinuation necessary for:
  - ANC < 400 cells/mm³
  - Active bacterial infection AND ANC < 500 cell/mm³
- Permanent discontinuation for neutropenia which is refractory to peginterferon dose reduction and filgrastim (G-CSF)
Level 1 Peginterferon Dose Reduction - neutropenia

• For ANC <500 but >400 cells/mm³
  • Peginterferon alfa-2a
    – Reduce dose from 180 to 135 mcg
  • Peginterferon alfa-2b
    – Reduce dose from 1.5 to 1.0 mcg/kg
• Maintain peginterferon dose at reduced level as subsequent increase will result in another ANC decline
• Monitor ANC at least weekly until stabilized
Level 2 Peginterferon Dose Reduction - neutropenia

• Further decline in ANC (but still above 400 cells/mm³) or lack of improvement in 14 days
• Peginterferon alfa-2a
  – Reduce dose from 135 to 90 mcg
• Peginterferon alfa-2b
  – Reduce dose from 1.0 to 0.5 mcg/kg
• Most experts would add filgrastim (G-CSF)
Use of Filgrastim (G-CSF)

- For ANC <500 cells/mm³
- Neutropenia which dose not respond to level 1 peginterferon dose reduction
- G-CSF 300 mcg SC once or twice weekly
- Monitor ANC at least 1-2X weekly
- Redose based on response
- G-CSF may need dosed 2-3x/week in some cases to maintain ANC >500 cells/mm³
- Hold G-CSF for ANC > 750 cells/mm³