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*

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Hepatitis C Treatment Expansion Initiative, Evaluation & Technical Assistance Center

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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 mf 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)

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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

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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/mm^3

Level 1 Peginterferon Dose Reduction - thrombocytopenia

- Platelets <40,000 but >25,000 cells/mm^3
- 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

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Level 2 Peginterferon Dose Reduction - thrombocytopenia

- Further decline in platelets (but still >25,000 cells/mm^3
- 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

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Management of Neutropenia

- Primary strategy is peginterferon dose reduction
- Permanent discontinuation rarely necessary, but temporary discontinuation necessary for:
  - ANC < 400 cells/mm^3
  - Active bacterial infection AND ANC < 500 cell/mm^3
- Permanent discontinuation for neutropenia which is refractory to peginterferon dose reduction and filgrastim (G-CSF)

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Level 1 Peginterferon Dose Reduction - neutropenia

- For ANC <500 but >400 cells/mm^3
- 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

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Level 2 Peginterferon Dose Reduction - neutropenia

- Further decline in ANC (but still above 400 cells/mm^3) 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/mm^3
- 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/mm^3
- Hold G-CSF for ANC > 750 cells/mm^3