Erythropoietin Treatment in Multiple Myeloma – Friend or Foe?

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Incurable plasma cell neoplasm - Monoclonal Ig
Lytic bone disease
Anemia (60–90%, response to rHuEPO – 80%)
Renal failure, Immune deficiencies; Infections; CNS involvement; Hypercalcemia; Amyloidosis
Clinical Observation

Several multiple myeloma patients treated with recombinant human EPO live(d) longer than expected, based on the stage of their disease (Mittleman et al., 1997, 2004)

Hypothesis

EPO has other biological effects in multiple myeloma patients (in addition to alleviating their anemia)
EPO and Multiple Myeloma

Multiple myeloma (MM) patients

- Prolonged survival, improved QOL *Mittelman et. al., 2004*
- Normalized CD4:CD8 cell ratio, improved T cell function *Prutchi-Sagiv et al., 2006*

MM Mouse models -

- MOPC-315, 5T2: EPO-induced tumor mass reduction and regression *Mittelman et al., 2001; Katz et al., 2005, 2007*
5T33 Multiple Myeloma Mouse Model

5T33 MM cells (IgG2bκ)

Diluent

EPO

MM Diluent

MM EPO

Days: 0.......8................. 18..20..22..24..27..29..31..34..36..38..41

5T33MM

EPO 30u

sacrifice

Naamit Deshet-Unger

IgG2b serum

ng/ml

0 100 200 300 400

Diluent MM

30,000 cells

5T33 Multiple Myeloma Mouse Model

Naamit Deshet-Unger
EPO-Induced Decrease in K- Light Chain

Kappa
22.5KDa

Lambda
22.5KDa

Days: 0 16 28 36

Bone marrow

Serum
after EPO stimulation

Plasma cells

IgG2b
immunoglobulin

Kappa light chain

IgA

N > 9
unpublished
EPO-Associated Maintenance of IgA Levels in MM Mice

Unpublished
EPO-Induced Increase in Bone Marrow Macrophages

Diluent

- % of cells: 61%
- CD11b+: 0.27%

EPO

- % of cells: 39.8%
- CD11b+: 0.91%

MM

- % of cells: 74.9%
- CD11b+: 0.27%

MM+EPO

- % of cells: 63.2%
- CD11b+: 0.75%

*unpublished*

F4/80+ CD11b+

- Diluent: 0.0104
- EPO: 0.0132
- MM: 0.0132
- MM+EPO: 0.0132

N > 7
EPO Effects on Immune System in MM

- Decreased MM progression, decreased paraprotein
- Stromal cells
- MM cells
- IFN-\(\gamma\)
  - Macrophages:
    - Activity and cell levels
    - Increased activity of acquired and innate immune responses
  - Th1 activities
- Increased activity of acquired and innate immune responses
Multiple Myeloma is Associated with Bone Resorption

How does EPO affect bones in MM Mice?

Dr. Sahar Hiram-Bab
EPO Treatment in Multiple Myeloma – Friend or Foe?

- B cell
- Kappa light chain IgA
- Macrophage
- Stromal cells
- MM cells
- EPO

Immune System

Bone Resorption

RANKL

EPO
EPO Trip

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Funding: Multiple Myeloma Foundation
EPO Effects on Bone in MM

- HSC
- MM cells
- BMP
- OPG
- RANKL
- osteoclast
- Activated osteoclast
- Osteoblasts
- Bone
- Macrophage
- EPO
- EPO-R

- EPO-R
- RANK
- Differentiation RANKL, MCSF
- ?
- ?
- ?
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- ?
- ?