Mantle-Cell Leukemia: Lessons in Life and Death

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Case Presentation

• 60 y.o. man PhD engineer inventor presented in December, 2003 with very enlarged spleen
• CBC: Hematocrit 26.7/Hgb 8.6
• WBC: 155,800 with 99% lymphocytes
• Platelet count: 59,000
• Bone Marrow Biopsy…
Low Power Bone Marrow Biopsy
High Power Bone Marrow Biopsy
Case Presentation, cont.

- Flow cytometry on bone marrow:
  - CD 20 +  CD 5 +
  - FMC7 +
  - CD23 –
- Cytogenetics: 11;14 translocation in 166/200 cells studied by FISH analysis
- Monoclonal λ light-chain on cell surface
- Diagnosis of Mantle Cell lymphoma/leukemia made on the above bases
Case Presentation, continued

• Treated with 6 cycles of “R-CHOP” and went into solid clinical remission with disappearance of splenomegaly and normalization of peripheral blood counts

• FISH not repeated on marrow or blood

• Referred to Bone Marrow Transplant Unit at MCV for consideration of high-dose therapy and stem-cell rescue
Case Presentation, continued

- At recommendation of MCV he received three additional cycles of higher intensity chemo consisting of Rituxan, Ifosfamide with Mesna, Carboplatin and Etoposide (R-ICE) to reduce amount of minimal residual disease prior to transplant
- Then went back to MCV for more chemo with stem-cell mobilization
In December, 2004 after much therapy and preparation he received his transplant:

- BEAM therapy (high-dose BCNU followed by high-dose ARA-C and etoposide followed by high-dose melphalan)
- Then he received stem-cell reinfusion

- Tolerated well; discharged from MCV on G-CSF and numerous antibiotics, anti-fungals and anti-virals
- Never developed a serious infectious complication
- Took months to recover his former vigor
Case Presentation, continued

- At his request, Bone-Marrow biopsy performed in April, 2005....
Case Presentation, continued

• At his request, Bone-Marrow biopsy performed in April, 2005: normal morphologically and by cytogenetics

• Deemed to be in hematologic and cytogenetic remission

• After much consideration and with considerable intellectual input from patient (risk-benefit analysis) he was treated with pulse maintenance Rituxan every six months for two years

• Continued well although developed periodic severe neutropenia usually associated with otherwise trivial viral infections
Case Presentation, continued

• In May, 2007 developed Herpes Zoster of face with some minimal disseminated zoster
• Felt ill with low-grade fever
• Admitted after failing to improve on oral Famvir
• Improved quickly on intravenous Acyclovir
• No post-herpetic neuralgia or other sequelae
Case Presentation

- In May, 2008, 3.5 years after ABMT he became ill again
- Admitted to hospital in California while traveling with severe bronchopneumonia
- Hematocrit 25 at that time
- By the next month his white count was rising rapidly and his disease was in obvious relapse
- Flow cytometry on peripheral blood confirmed same malignant cells as with original presentation
Case Presentation, continued

- Admitted to Maryview ill for re-induction with R-CHOP
- Because of persistence of respiratory symptoms CT scan done which revealed multiple pulmonary emboli....
- Anticoagulated gingerly in light of low platelet count
- WBC fell quickly but rose again before he could be retreated....functionally R-CHOP resistant
Case Presentation, continued

- Referred back to MCV
- He arrived at MCV with pneumonia, was hospitalized there and convalesced slowly
- Grew *e. coli* and a fungus from his blood
- Before he could be re-treated (this time with Velcade and Rituxan) he was admitted to Maryview with mental-status deterioration and found to be in renal failure
Case Presentation, continued

- Evaluation of renal failure included imaging studies to rule out obstruction and vigorous rehydration to rule out volume depletion as contributing factor
- X ray studies....
Bilateral pulmonary infiltrates – pneumonia vs. CHF
Normal-sized kidneys with normal collecting systems
Case Presentation, continued

- Evaluation of renal failure included imaging studies (see above) to rule out obstruction and vigorous rehydration to rule out volume depletion as contributing factor.
- Clinical diagnosis of lymphomatous infiltration of kidneys as cause of uremia entertained as diagnosis of exclusion, with literature support.
- Family at this point insisted that aggressive measures be withdrawn and he died peacefully on July 22, 2008.
- Autopsy performed...
Retroperitoneal Lymph Node – extensive infiltration with lymphoma
Kidneys – infiltrated with lymphoma, enough to cause renal failure
Spleen – normal architecture replaced by diffuse lymphomatous involvement
Liver – focally infiltrated with lymphoma
Lungs – focal perivascular infiltration
Cause of Death

• Organ failure secondary to infiltration with Mantle-Cell lymphoma
• Despite altered mental status there was no evidence of CNS lymphoma – either in meninges or parenchyma of brain
Mantle-Cell Lymphoma/Leukemia

- B-cell neoplasm of moderately aggressive nature
- Characteristic flow-cytometric and cytogenetic abnormalities
  - CD5, CD20, FMC7 positivity
  - CD23 negative….our patient exhibited conformity with these
  - Surface membrane IgM and IgD: \( \lambda \) (also seen although parent Ig class not determined)
  - 11;14 translocation almost always present although not completely diagnostic (can be seen in other NHL’s)
Mantle-Cell Lymphoma, continued

- Cell morphology not pathognomonic of diagnosis
- Lymph-node appearance, when sampled, is helpful in the diagnosis
  - Can be nodular or diffuse
Prognosis of MCL

• Investigated as separate entity in one large study
• Resulted in development of “MIPI” scoring
• Multivariate analysis as to prognosis…
## Summary of Prognostic Factors

*n=455; from Hoster et al BLOOD 111:558, 2008*

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<td>LDH</td>
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Prognosis Over Time

*LDH never measured but likely high
Decision to Transplant

- Natural history of disease optimally treated without transplant suggested five-year survival likelihood of 10-30%
- Transplant data reasonably robust and optimistic for patients in first remission (vs. transplant after first relapse)
- Age worrisome but he was physiologically youthful
Long-Term Results from Autologous Hematopoetic Stem-Cell Transplant in MCL

**Fig 1.** Overall survival from time of transplantation by disease status.

From Vandenberghe *Br J Haematology* 120:793, 2003
Analysis by Age – Small Numbers but Sobering

Fig 4. Overall survival and age (years) at diagnosis.

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p=0.041 for age > vs. < 60
RW: Lesson in life and death

- Remarkable individual who showed courage and grace throughout his illness
- Continued to work on his engineering projects involving building machines working at the nano-particle level
- Was able to become a functioning member of the team through his extraordinary intellectual curiosity
  - Most of the time this is a speed bump for oncologists…not here
- Great personal loss for me, as he became a friend as well as patient
Lessons, continued

• Tumor burden at autopsy enormous
• Clinical condition belied extent of disease until the very end
• Speed of relapse and organ infiltration was very rapid – leaving his clinical team behind the curve in assessing and treating
• Unlikely to have achieved long-term survival regardless given resistance of his emerging cell line – despite being identical by flow cytometry to original cells
From First Ten Ångstroms Website
At his Christmas party while in remission
For a copy of this talk....

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