WALDENSTROM MACROGLOBULINEMIA: AN EXCITING, UPBEAT STORY

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Disclosures for Morton Coleman, MD

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<th>Category</th>
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<td>Employment</td>
<td>None</td>
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<td>Consultancy</td>
<td>Celgene, GlaxoSmithKline, Millenium, Gilead</td>
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<td>Equity Ownership</td>
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<td>Research Funding</td>
<td>Glaxo Smith Kline, Onyx, Gilead, Pharmacyclics, Abbvie, Celgene</td>
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## Disclosures for Morton Coleman, MD, con’t

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<tr>
<td>Speakers Bureau</td>
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THE CUP IS HALF EMPTY: WALDENSTROM MACROGLOBULINEMIA IS A RARE DISEASE
The Frequency of Various Lymphoma Subtypes in Adults

Follicular (22%)
Diffuse large B cell (31%)
Mantle cell (6%)
Peripheral T cell (6%)
Other subtypes with a frequency ≤2% (9%)
Composite lymphomas (13%)
Small lymphocytic (6%)
Marginal zone, B cell, MALT type (5%)
Marginal zone, B cell, nodal type (1%)
Lymphoplasmacytic (1%)

MALT=mucosa-associated lymphoid tissue.
waldenstom macroglobulinemia is ‘halfway’ between lymphoma and myeloma
Cell Maturation and Neoplasms

- Pre-B
- Early B
- Mature B
- Activated B
- Plasma
- +CD5
- CD19
- CD20
- CD22
- CD52

±CD5

ALL = acute lymphoblastic leukemia; PLL = prolymphocytic leukemia; HCL = hairy cell leukemia; WM = Waldenström’s macroglobulinemia; MM = multiple myeloma.

http://www.clinicalflow.com/@api/deki/files/348/=b_cell.jpg
THE CUP IS HALF FULL:
MEDICINES WHICH WORK FOR MYELOMA OFTEN TO THE EXCLUSION OF LYMPHOMA AND VICE VERSA BOTH WORK IN WALDENSTROM MACROGLOBULINEMIA
CANCER DRUG DEVELOPMENT

1945 - 2000

Total # Approved Drugs

1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000

Cyclophosphamide
Doxorubicin
Vincristine
Cyclophosphamide
Nitrogen Mustard

Paclitaxel
Topotecan
Carboplatin
Ifosfamide
Rituximab
Herceptin
Gemtuzumab

Courtesy Owen A. O'Connor
WHAT IS AN ANTIGEN?

AN ANTIGEN IS AN IDENTIFYING SUBSTANCE ON THE SURFACE OF CELLS, BACTERIA, VIRUSES, ETC. THAT IS RECOGNIZED BY THE BODY’S IMMUNOLOGIC DEFENSES. THE BODY THEN MOUNTS A DEFENSE OF WHICH ONE IS ANTIBODIES DIRECTED AGAINST THE ANTIGEN. THINK THE STATUE OF LIBERTY AND THE EMPIRE STATE BUILDING WHICH IDENTIFY NEW YORK CITY. THE ANTIBODY-ANTIGEN REACTION IS LIKE A LOCK AND KEY.

SOMETIMES THE BODY DOES NOT RECOGNIZE THE ANTIGENS ON SOME OF ITS OWN CELLS AS ‘SELF’. DISEASES AS A RESULT OF THIS NON-RECOGNITION IS CALLED ‘AUTOIMMUNE DISEASES’.
PROTEIN ELECTROPHORESIS

Normal pattern

Reference ranges:

- Total protein: 6.0 - 8.0 g/dL
- Albumin: 3.5 - 5.0 g/dL
- α1-globulins: 0.1 - 0.4 g/dL
- α2-globulins: 0.4 - 1.3 g/dL
- β-globulins: 0.6 - 1.3 g/dL
- γ-globulins: 0.6 - 1.5 g/dL
M (MONOCLONAL) SPIKE

Protein Electrophoresis

- Protein electrophoresis

Normal SPEP

Myeloma cells producing M spike
TWO BLOCKBUSTER DEVELOPMENTS

BLOCKBUSTER DEVELOPMENT ONE:
RITUXIMAB AND THE DEVELOPMENT OF OTHER MONOCLONAL ANTIBODIES DIRECTED AGAINST ANTIGEN CD 20 (ALONG WITH OTHER ANTIBODIES IN DEVELOPMENT AGAINST OTHER ANTIGENS: CD 19, CD22, CD38 ETC.).
B-Cell Maturation and Neoplasms

ALL = acute lymphoblastic leukemia; PLL = prolymphocytic leukemia; HCL = hairy cell leukemia; WM = Waldenström’s macroglobulinemia; MM = multiple myeloma.

http://www.clinicalflow.com/@api/deki/files/348/=b_cell.jpg
OUR BETTER UNDERSTANDING OF THE B CELL RECEPTOR AND OTHER SIGNALING RECEPTORS ON THE SURFACE OF THE CELL THAT INFORM THE B CELL TO LIVE, GROW, AND DIVIDE. THE SIGNAL IS SENT FROM THE RECEPTORS (e.g. ALONG THE MYD-88 PATHWAY WHICH IS ALMOST ALWAYS ACTIVATED IN WM) FROM ONE ‘NODE’ TO THE NEXT UNTIL THE SIGNAL TELLS THE NUCLEUS TO INSTRUCT THE CELL TO THRIVE AND DIVIDE. THINK PONY EXPRESS.
Our better understanding of the B cell receptor and the signaling pathways that inform the B cell to live, grow, and divide has allowed the development of signaling inhibitors, two of which are already on the market. The signaling inhibitor Imbruvica interferes with Bruton’s tyrosine kinase which interacts with the pathways of MyD88, seen in almost all Waldenstrom Macroglobulinemia patients. Think Pony Express.
Targeting the “BCR++” Antigen Pathway:
OUR BETTER UNDERSTANDING OF THE B CELL RECEPTOR AND THE SIGNALING PATHWAYS HAS ALLOWED THE DEVELOPMENT OF SIGNALING INHIBITORS, TWO OF WHICH ARE ALREADY ON THE MARKET. THE SIGNALING INHIBITOR IMBRUVICA INTERFERES WITH BRUTAN’ S TYROSINE KINASE WHICH INTERACTS WITH THE PATHWAYS OF MYD88, SEEN IN ALMOST ALL WALDENSTROM MACROGLOBULINEMIA PATIENTS.
THE B CELL RECEPTOR AND MYD 88 PATHWAYS

Chronic active BCR signaling

Constitutive MYD88 signaling

Autocrine interferon signaling

CD79A/B ITAM mutation

MYD88 TIR domain mutation

CD79A/B coiled-coil mutation

NF-κB pathway

Lenalidomide

Survival

Interferon pathway

Death

BRUTAN’S TYROSINE KINASE MULTIPLE FUNCTIONS and proliferation

- BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion\textsuperscript{1-5}
- Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro

RESPONSES TO THE BLOCKBUSTERS

RITUXIMAB: ~50%, ALMOST NO MARROW SUPPRESSION, GREATLY AUGMENTS THE EFFICACY OF OTHER MEDICINES

IBRUTINIB: ~90%, RELATIVELY LITTLE MARROW SUPPRESSION
OTHER MONOCLONAL ANTIBODIES: TARGETED THERAPY

ANTI-CD 20:
OFATUMUMAB, OBINTUZUMAB

ANTI-CD 38:
DARATUMUMAB

COMING DOWN THE PIKE:
ANTI-CD19, IMMUNOTOXINS,
COMBINATIONS OF ANTIBODIES
Novel BCR Acting Agents

**BTK:**
- IBRUTINIB (PCI-32765)
- CC-292 (AVL-292)
- ACALABRUTNIB (ACP-196)

**PI 3 Kinase:**
- IDELALISIB (GS-1101, CAL-101)
- IPI-145
- COPANLISIB (BAY 80-6946)

**SYK:**
- fostamatinib (R935778)
- PRT062070
OTHER ‘NOVEL’ APPROACHES

PROTEOSOME INHIBITORS:
BORTEZOMIB, CARFILZOMIB

IMIDS: THALIDOMIDE, LENALIDOMIDE, POMILIDOMIDE

MTOR INHIBITOR: EVEROLIMUS

CHEMOTHERAPY: BENDAMUSTINE

HDAC INHIBITOR: PANOBINOSTAT

IMMUNOLOGIC ‘ATTACK’: CAR-T,
CHECKPOINT INHIBITORS
CHECKPOINT INHIBITION
VENETOCLAX IS A POTENT BCL-2 INHIBITOR. BCL-2 IS A GENE PRODUCT WHICH PREVENTS APOPTOSIS, PROGRAMMED CELL DEATH (AS OPPOSED TO NECROSIS, SUDDEN OR ACCIDENTAL CELL DEATH AS FROM LACK OF OXYGEN).

BCL2 AND BAX ARE OPPOSED TO EACH OTHER. BAX PROMOTES CELL DEATH. THINK YIN AND YANG.
TUG OF WAR
BCL VS. BAX
ANTI-APOPTOSIS VS. APOPTOSIS
THE CONUNDRUM: A SURFEIT OF RICHES

WITH ALL OF THESE EXCITING NEW MEDICINES COMING DOWN THE PIKE HOW DO WE COMBINE THEM WITHOUT UNDUE TOXICITY? DO WE GIVE THEM TOGETHER OR IN SEQUENCE? GIVEN ALL THE ‘COMBINATIONS AND PERMUTATIONS’ WE MAY HAVE MORE OPTIONS THAN PATIENTS!
A NEW DAWN IS RISING FOR WM
THANK YOU FOR YOUR ATTENTION