Serum BCMA: A Novel Biomarker for Monitoring and Predicting Outcome for Patients with B-Cell Malignancies

Institute for Myeloma and Bone Cancer Research
West Hollywood, CA

OncoTracker
West Hollywood, CA
Financial Disclosures

• OncoTracker
  – Founder
  – Stock ownership
B-Cell Maturation Antigen (BCMA)

- TNF receptor (TNFR) family member
  - Normal B-cells
  - Malignant B-cells
    • Multiple myeloma (MM)
- BAFF (B-cell activating factor) and APRIL (a proliferation inducing ligand) are its ligands and TNF family members
  - These ligands activate cell proliferation pathways and upregulate antiapoptotic proteins in
    • MM cell lines
    • B-cells
    • T-lymphocytes
Serum B-Cell Maturation Antigen (BCMA) in Patients w/ Monoclonal Gammopathies

- Other soluble TNFRs have been found among pts w/ MM and other diseases (e.g. sIL-6R)
- BCMA is highly expressed on tumor cells from pts w/ B-cell malignancies

Thus, we determined whether BCMA was found in serum of pts w/ multiple myeloma using a polyclonal anti-BCMA ELISA-based test

If present, relationship of serum levels to
- type of monoclonal gammopathy
- standard markers for monitoring
- clinical status of MM pts
- PFS and OS
- their immune deficiency
Serum BCMA Levels in Patients with Monoclonal Gammopathies

Median Serum BCMA Levels (ng/mL):
- Healthy Donors: 37.9 (range, 14.1-958.1)
- MGUS: 53.6 (range, 11.7-693.3)
- Smoldering MM: 85.1 (range, 31.6-2956.0)
- Active, Untreated MM: 521.6 (range, 17.8-9027.0)

p-values:
- Healthy Donors vs MGUS: p=0.0109
- Healthy Donors vs Smoldering MM: p<0.0001
- Healthy Donors vs Active, Untreated MM: p<0.0001
- MGUS vs Smoldering MM: p=0.0006
- MGUS vs Active, Untreated MM: p<0.0001
- Smoldering MM vs Active, Untreated MM: p<0.0001
Serum BCMA Correlates with M-Protein Levels in Individual MM Patients

Ghermezi et al. Blood 2014
BCMA vs Clinical Course in Nonsecretory MM Patients

Pt. 2460

- PET: + at 3
- PET: SUV decreased to 2
- PET: -

Pt. 1977

- PET: +
- PET: -
- PET: -
- PET: -
- PET: -

BCMA (ng/ml) vs Clinical Course in Nonsecretory MM Patients
Progression-free Survival of MM Patients Based on BCMA Levels Prior to Start of New Treatment (n=187)

- **Range (ng/mL):**
  - Below median: 14.39 – 320.31
  - Above median: 332.56 – 23051.74

- **Median BCMA:** 332.56 ng/mL
  - **Range (ng/mL):**
    - Q1 – Q3: 14.39 – 976.73
    - Q4: 1000.10 – 23051.74
  - **Quartile 4 BCMA cutoff:** >988.42 ng/mL

- **Median PFS:**
  - Below median: 9.0 months
  - Above median: 3.6 months
  - **Q1-Q3:** 7.2 months
  - **Q4:** 2.1 months
Overall Survival from the Time of First Determination of Serum BCMA Level (n=241)

Range (ng/mL): Below median: 14.39-275.33
Above median: 288.54-23051.74

Median BCMA = 136.2 ng/mL

Range (ng/mL): Q1 – Q3: 14.39-968.94
Q4: 976.67-23051.74

Median PFS:
Below median: 96.0 months
Above median: 87.0 months

Median PFS:
Q1-Q3: 87.0 months
Q4: 47.0 months
Soluble BAFF Binds BCMA on B-Cells Leading to Antibody Production
Hypothesis: Serum BCMA Binds Its Ligand BAFF Preventing It from Binding to BCMA on B-Cells Development Resulting in a Reduction in Antibody Levels
BCMA Correlates w/ Tumor Volume in SCID Mice Bearing Human MM Xenografts
Plasma from SCID Mice w/ Human MM Xenografts show BCMA-BAFF Complexes

Absorbance (OD 450 nm)

MM Xenograft BCMA-BAFF Complexes

- LAGκ-1A (P = 0.0025)
- LAGκ-2 (P = 0.0004)
- LAGλ-1 (P = 0.0374)
- SCID plasma
- SCID control 1
- mBAFF cap w/o SCID plasma
- hBCMA detec w/o SCID plasma
SCID Mice Bearing Human MM Show Reduced Free BAFF Levels
C57Bl mice (3.25 month old)

Immune Competent Mice Injected w/ BCMA Show Reduced Ig Levels

Days Post-BCMA-Fc Injection
IgM Level (mg/dL)

-1 0 1 2 3 4 5 6 7
0
10
20
30
40
50
60
BCMA-Fc
Ig-Fc Control
Untreated Control

Tx

P = 0.0088
P = 0.0001

Tx

P = 0.0001
P = 0.0088
BCMA-BAFF Complexes Are Present in Serum of MM Patients

OD (450 nm)

MM # 1
MM # 2
BCMA-Fc (2 ng/ml)
BAFF (2.5 ng/ml)

BCMA = 231 ng/ml
Negative Controls
Antibody controls
BCMA = 264 ng/ml

BCMA-BAFF Complexes in MM Patients
Recombinant Human BCMA and Myeloma Serum Reduce BAFF Binding to Raji B-Cells

Isotype Control
(Mouse IgG-FITC)

Experimental Control
(rh-BCMA+Anti-flag-FITC)

Experimental Control
BAFF-his-Flag-Tag+mouse IgG-FITC

Experimental Control
Anti-flag-FITC

BAFF-his-Flag-Tag
Anti-flag-FITC

BAFF-his-Flag-Tag
rhBCMA+anti-flag-FITC

rhBCMA+anti-BCMA antibody
+anti-flag-FITC

BAFF-his-Flag-Tag
MM-serum+anti-flag-FITC

BAFF-his-Flag-Tag
MM-serum+anti-BCMA antibody
+anti-flag-FITC

Anti-BCMA antibody restores BAFF binding to Raji cells
IgG MM: Uninvolved IgA Levels are Inversely Correlated w/ BCMA Levels

Mann-Whitney p value = P < 0.0001
Significant (p < .05): yes

Total = 134
Normal IgG = 16
<Normal IgG = 118
Waldenstrom’s Macroglobulinemia*: Serum BCMA

Serum BCMA Levels of Waldenström's macroglobulinemia Patients vs Healthy Subjects

Median BCMA Levels (ng/mL):
WM: 79.53
Healthy Subjects: 36.03

p<0.0001***

*Pts from DFCI (Steve Treon) and James R. Berenson, MD
Clinical Status vs Serum BCMA Levels in Patients with Waldenström's macroglobulinemia

- **p-value:**
  - PD vs ≥ PR: 0.0004***
  - SD vs ≥ PR: 0.0229*

- **Median Values (ng/mL):**
  - ≥PR: 26.2
  - SD: 76.2
  - PD: 84.1
CLL: Plasma BCMA

- Plasma samples from 171 CLL patients obtained from UCSD CLL Plasma Bank
  - from Drs. Tom Kipps and Laura Rassenti
- Plasma BCMA levels determined
- Correlate levels with:
  - Aggressive vs Indolent CLL based on usual biomarkers
    - ZAP70
    - Ig mutational status
    - Cytogenetics
  - Time to first treatment
  - Overall survival
  - Changes in individual patient’s response to treatment
Plasma BCMA Levels of Patients with Untreated CLL vs. Healthy Subjects

Median BCMA Levels (ng/mL):
- Untreated CLL: 73.15
- Healthy Subjects: 36.03

p-value <0.0001***
Plasma BCMA Levels in Patients with Indolent CLL vs. Aggressive CLL vs. Healthy Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Median BCMA Levels (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indolent</td>
<td>87</td>
<td>42.13</td>
</tr>
<tr>
<td>Aggressive</td>
<td>84</td>
<td>87.46</td>
</tr>
<tr>
<td>Healthy Subjects</td>
<td>104</td>
<td>36.03</td>
</tr>
</tbody>
</table>

p-value:
- Indolent vs. Aggressive: <0.0001***
- Indolent vs. Healthy Subjects: 0.0079**
- Aggressive vs. Healthy Subjects: <0.0001***
**Time To First Treatment Based on Plasma BCMA Levels**

- **Quartiles 1, 2, and 3 (n = 125)**
- **Quartile 4 (n = 42)**

Median Time to Tx (p<0.0001):
- Quartiles 1, 2, and 3: 44.6 months
- Quartile 4: 8.0 months

BCMA highest quartile (ng/mL): > 104.45
CLL

Started HDMP + Rituximab
3/2/05

Not Treated

Partial Response
CLL

Not Treated

Fludarabine + Rituximab

Complete Response MRD (-)

BCMA (ng/ml)

AGGRESSIVE

44AC FIRST 8/2/2005

44C-S2 SECOND 8/21/2007

44C-S3 POST TX
Overall Survival Based on Plasma BCMA Levels

BCMA highest quartile (ng/mL): > 105.8

p = 0.034
**Plasma BCMA Levels vs. IvGH % Homology**

- **Median BCMA Levels (ng/mL):**
  - ≤ 98% Homology: 42.59
  - > 98% Homology: 87.54

- **n Values:**
  - ≤ 98% Homology: 88
  - > 98% Homology: 83

- **p Value:** $p = <0.0001^{***}$
Plasma BCMA Levels vs. ZAP-70 Expression

Median BCMA Levels (ng/mL):
≤ 20% ZAP-70 Expression: 42.59
> 20% ZAP-70 Expression: 87.38

n = 88

p = <0.0001***
Plasma BCMA Levels vs. Chromosome 13 Status

Median BCMA Levels (ng/mL):
- Normal: 73.80
- Deletion: 46.57

n = 77
n = 83

p = 0.0002
Summary

• We first reported soluble BCMA in the blood
• BCMA levels are elevated in serum from MM & WM patients and plasma from CLL patients
  – Aggressiveness of the disease (CLL)
  – Correlate with clinical status (Response vs PD)
  – Can be used to track response to treatment
  – Predict progression-free and overall survival
• SCID mice bearing human MM xenografts, even with nonsecretory tumors, show the presence of human BCMA in their plasma
  – Levels correlate with tumor size
Summary (cont’d)

• BCMA-BAFF complexes found in
  – plasma from SCID mice bearing human MM xenografts containing human BCMA
  – MM pt serum

• MM serum blocks binding of BAFF to Raji B-cells

• Serum BCMA inversely correlates w/ BAFF and polyclonal Ig levels in MM patients

• Recombinant BCMA administered to immune competent mice reduces Ig levels

• Thus, circulating BCMA in MM pts binds BAFF
  – prevents B-cell function and plasma cell development
    • results in reduced polyclonal Ig levels, a hallmark of MM