Improved Survival: What Trade-offs Make Sense?

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Disclosure Information

• I have no financial relationships to disclose.
• I will not discuss off-label use and/or investigational use in my presentation.
Liver Injury in Oncology

• Several challenges specific to oncology
• Sick patients; multiple confounders
• Attribution is difficult
• Sub-optimal work-ups
• Bottom line: Efficacy trumps all
Case study

• 54 y.o. female from India with heavily pre-treated metastatic breast cancer
  – PMH: HTN, hypothyroid
  – liver metastases: 1.4, 3.3, 6.0 cm
  – Day -8: screening ALT 39, AST 42, TBIL 1.2
  – Cycle 1 Day 1: baseline ALT 68, AST 70, TBL 1.4 → received one dose of I.V. study drug on phase 3 trial*
  – Cycle 1 Day 5: Jaundice (Gr4 bilirubin), AMS
  – Cycle 1 Day 6 : ALT 159, AST 820, TBL 12.8, cre 2.3, NH3 78
  – Cycle 1 Day 7: Died. No autopsy. No testing for acute hepatitis.
  – Fatal fulminant liver failure related to study drug per investigator

* Unclear if investigator knew of rising liver tests prior to dosing, but still acceptable numbers as per protocol

Courtesy Gideon Blumenthal, M.D.
### Case study (continued)

<table>
<thead>
<tr>
<th></th>
<th>ALT (xULN)</th>
<th>AST (XULN)</th>
<th>TBILI (XULN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day -8</td>
<td>0.8</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Day 1</td>
<td>1.4</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Day 5</td>
<td>3.2</td>
<td>16.4</td>
<td>12.8</td>
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Would an unacceptable rate of ALT rise \((68-39)/8 = 3.6\) IU per day have been useful to screen out “bad actors”?

Courtesy Gideon Blumenthal, M.D.
Threshold for Hepatotoxicity

• Need to consider risk/benefit
• High threshold in metastatic disease
• Lower threshold in non-invasive disease, chemoprevention, or neo-adjuvant/adjuvant therapy
  – Shorter allowable duration, lower allowable elevations
Biologics and Immunotherapies

Given differences in ADME, conventional approaches to evaluate DILI in small molecule drugs may not apply

- Liver injury may be due to on-target unintended toxicities rather than xenobiotic injury
- We have no data that Hy’s Law in Mabs predicts hepatic failure/death
- Further evaluation needed prior to extrapolation
- Does adaptation/tolerance occur differently or at all compared to SMDs?
- What factors predict likelihood of liver failure? Need better understanding of pathophysiology and time-course of liver injury
Combination Immunotherapies

- Synergistic hepatotoxicity?

- Vemurafenib
  - Metabolized largely through CYP1A2
  - 3% AST/ALT >5x ULN
  - ?Toxic intermediate

- Ipilimumab
  - Immune-mediated hepatitis 3.8%
  - Both hepatocellular and bile duct injury reported

- Vemurafenib + Ipilimumab phase I in patients with BRAF-mutated metastatic melanoma
  - No theoretical DDI or overlapping toxicity
  - 1 month of vemurafenib run-in at full dose + 4 infusions of ipilimumab
  - DLT in 4/6 patients in 1st cohort (G3 AST/ALT 2-5 weeks post ipilimumab)
  - Aminotransferase elevations in 3/4 patients in lower-dose vemurafenib cohort
  - Two cases of Hy’s Law
Immunotherapy + TKI
Choice of Partner

- Sunitinib
- Pazopanib
- Axitinib
- Nivolumab
- Pembrolizumab

Legend:
- Grade 3/4 ALT
- w/ Nivo
- w/ Pembro
Clinical Trial vs “Real World”

• Small sample size
• Healthier patients
• Fewer concomitant medications
• Homogenous (ethnic, geographic, age)
Regulatory Considerations

• Identification of susceptible subpopulations
  – History of autoimmunity?
  – Hepatic reserve
  – Polymorphisms
    • HFE -> pazopanib
    • HLA-DRB1*07:01/DQA1*02:01 -> lapatinib
Wish List

• Organ dysfunction studies
• Long-term follow-up/post-marketing assessments
• Real world data
  – COTA (mostly academic), Flatiron (mostly community)
  – De-identified patient information
Concluding Remarks

• Efficacy is key, clinical context is important
  – Identification of susceptible subgroups

• We should strive for better diagnostic DILI workup
  – Exclude other causes
  – Liver biopsy
  – Autopsy
  – recommendations for eligibility, dose modification, dose discontinuation, diagnostic DILI workup (excluding other causes, liver biopsy, autopsy)
  – drug labeling

• Additional caution may be warranted with immunotherapy combinations

• Flexible criteria beyond Hy’s Law may be needed depending on drug mechanism and benefit/risk ratio