Selected Viruses
Overarching Issues

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NTP Peer Review Meeting
December 17, 2015
• Issues

  – High prevalence of infection (EBV, MCV)
  
  – Cofactors may affect cancer outcome: e.g., immunosuppression, other infectious agents, host genetics
  
  – Cancer endpoint defined by the presence of virus (adult T-cell leukemia/lymphoma and HTLV-1 or primary effusion lymphoma and KSHV).
Factors to Consider

• Human epidemiology studies
  – Hill considerations

• Molecular information (clinical studies)
  – Monoclonality of virus in malignant tissue, e.g., (1) clonal immunoglobulin gene rearrangements (EBV), (2) size of the fused terminal repeat region is specific for each viral clone (KSHV and EBV), or (3) integration pattern of provirus into host chromosome DNA (HTLV and MCV).
    • Supports causality
    • Supports temporality
      – Evidence that the virus is expressing oncogenic protein.
      – Percentage of tumors positive for virus.
Draft RoC Monograph
Human T-Cell Lymphototropic Virus Type 1

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Human T-Cell Lymphotrophic Virus Type 1

Outline

Properties and detection
Transmission and exposure
Mechanistic information
Human cancer studies
Preliminary level of evidence summary
HTLV-1 Properties and Detection

• Retrovirus, single stranded RNA virus, enveloped
  – Four subtypes: HTLV-1, HTLV-2, HTLV-3, HTLV-4
  – HTLV-1 is only subtype associated with neoplasia

• Detection
  – Antibodies, DNA or RNA, in culture
  – Proviral load (amount of viral DNA/cell) correlates with disease onset
Significant U.S. Exposure

- HTLV-1 – U.S. blood donors (2000–2009) seroprevalence 0.0051% or approximately 16,000 people
  - Immigration can raise numbers in local populations in U.S.
  - In endemic areas – S.W. Japan, Caribbean Basin, Melanesia, parts of Africa, South America – prevalence can be 15%
  - Estimates of 15-20 million people infected worldwide

- Transmission
  - Transfer of infected body fluids such as semen and blood
  - Mother to child transmission – *in utero* and through breast milk
    - Breastfeeding has higher rate of transmission
Infects mainly CD4 T cells; ~5% of HTLV-1 carriers develop adult T-cell leukemia/lymphoma
~5% of HTLV-1 carriers develop adult T-cell leukemia/lymphoma

Tax
- Shown to immortalize human T cells both in vitro and in vivo in the absence of other viral factors
- Interacts with NF-kappaB proteins involved with T-cell proliferation, growth, survival
- Immunogenic
~5% of HTLV-1 carriers develop adult T-cell leukemia/lymphoma (ATLL)

HTLV-1 basic leucine zipper factor (HBZ)
- Maintains ATLL transformation
- Promotes immune evasion, cell survival, cell proliferation, and immortality
- Not immunogenic

Pathogenesis of Adult T-cell Leukemia/Lymphoma

HTLV-1

Matsuoka and Jeang, April 2007
Assessment of Four Cancer Endpoints

- Adult T-cell leukemia/lymphoma
- Liver cancer
- Gastric cancer
- Cutaneous T-cell lymphoma
  - Inconsistent evidence, inadequate to assess.
### Epidemiology

**Positive associations**

Originally link established by case reports/case series; over 550 cases primarily from Japan and South America (1985–2005)

HTLV-1 carriers developed ATLL (8 cohorts)

Risk higher with higher viral load or proviral load in 4 case-control studies nested in HTLV-1 cohort studies

### Human tissue

<table>
<thead>
<tr>
<th>Clonality</th>
<th>Monoclonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>% HTLV-1 infected tumors</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>HTLV-1 protein expression</td>
<td>40% Tax, 100% HBZ</td>
</tr>
<tr>
<td>Other</td>
<td>Diagnostic criteria for ATLL</td>
</tr>
</tbody>
</table>
**Limited level of evidence from human studies**

<table>
<thead>
<tr>
<th><strong>Epidemiology</strong></th>
<th>Positive associations in all studies (4 case-control and 2 cohort studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive associations</td>
<td></td>
</tr>
<tr>
<td>Positive findings in studies that excluded or controlled for history of blood transfusion</td>
<td></td>
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<tr>
<td>One study found HTLV-1 increased risk of HCV-associated cancer in men</td>
<td></td>
</tr>
<tr>
<td>Exposure-response (increasing risk with increasing antibody level found in one study)</td>
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<tr>
<td>Consistent evidence of increased risk but bias and confounding can not be ruled out.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Human tissue</strong></th>
<th>No available information</th>
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</thead>
<tbody>
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OR = odds ratio
## Decreased risk from human studies

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<tr>
<th><strong>Epidemiology</strong></th>
<th>Decreased risks in 3 cohort and 1 case-control study</th>
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<tbody>
<tr>
<td>Positive associations</td>
<td><em>Helicobacter pylori</em> positivity lower in HTLV-1 group compared with negative group</td>
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Sufficient evidence for adult T-cell leukemia/lymphoma (ATLL)

- Only HTLV-1 carriers develop ATLL
- Higher risk with higher viral load
- Monoclonal virus in tumors
- 100% HBZ and 40% Tax expression
  - Tax promotes T-cell proliferation, growth, survival
  - HBZ maintains ATLL transformation and immortality

Limited evidence for liver cancer

- Positive, non-significant associations with HTLV-1 infection
Clarifications?
All sections: Comment on whether the information is clear and technically accurate and identify any information that should be added or deleted,

Properties, Detection and Human Exposure

– and whether adequate information is presented to document past and/or current human exposure.

Human Cancer Studies

– and provide any scientific criticisms of NTP’s cancer assessment of the epidemiologic studies of exposure to the virus.

Mechanistic and Other Relevant Data

– and provide any scientific criticisms of the NTP’s synthesis of these data assessing effects of the virus.
Level of Evidence Conclusion (Vote)

Sufficient evidence of carcinogenicity from studies in humans

- Cancer sites with sufficient evidence
  - Adult T-cell leukemia/lymphoma

- Cancer sites with limited evidence
  - Liver cancer
Human T-cell lymphotropic virus type 1 (HTLV-1) is known to be a human carcinogen based on sufficient evidence from studies in humans. This conclusion is based on evidence from epidemiological and molecular studies, which show that HTLV-1 causes adult T-cell leukemia/lymphoma, and on supporting mechanistic data. There is also limited evidence for an association with liver cancer.
Draft Substance Profile

• Contains NTP’s preliminary recommendation of the listing status of the substance

• Summarizes the scientific information that is key to reaching a recommendation

• Provides information on properties, use, production, and exposure

• Provides information on existing federal regulations and guidelines
Peer Reviewer Comments

• Provide any new comments (e.g., not previously provided on the same facts or issues in the cancer hazard evaluation section) on whether the information on properties and detection, human exposure, cancer studies in humans and mechanistic data is clear and technically accurate.

• Comment on whether the substance profile highlights the information on cancer studies in humans and mechanistic data that are considered key to reaching the listing recommendation.