November 2014

Radiation Oncology Rotation, OHSU
NK-T Cell Presentation

David Routman, MS4
Case Report
HPI: 44 y/o M referred to LAC+USC from OSH

Initially presented with:

- Hearing loss
- One episode of epistaxis w/ persistent bleeding lasting > 5 minutes
- Nausea with increased salivation
- Dysphagia, odynophagia x 3 months
- Concurrent 80lb weight loss
- Endorsed fever
- Denies vomiting, chills, or nights sweats
Case - Presentation (cont’d)

**PMH:** Denies

**Allergies:** NKDA

**Medications:** None

**FHx:** Denies any history of malignancy

**SHx:** Denies any tobacco or illicit drug use. Drinks social EtOH, no history of abuse. Lives with his family

**PE:**

VS: 100.2 deg, 109/73, HR 123, RR 16, 144lbs, 5'7"
GEN: NAD, thin, muffled voice, alert/oriented x 3
HEENT: Left posterior OP with ulcerating mass, coated with white film, foul odor, no large neck mass
CHEST: CTAB, tachycardia, reg rhythm
ABD: NTND, soft
EXT: No edema
Extranodal NK/T Cell Lymphoma

Diagnosis
Epidemiology
Pathogenesis
Extranodal NK/T Cell Lymphoma Overview

Previously Known As:
- Lethal midline granuloma
- Midline malignant reticulosis
- Angiocentric lymphoma

Characteristic features:
- Angioinvasion and Angiocentrism
- Necrosis
- Positive for Epstein-Barr virus (EBV) (>95% of the time)
- Usually associated with a natural killer (NK) cell phenotype
- T cell nomenclature reflects ambiguity in its cellular origins

Patient population:
- Most common in Asia and Central and South America
- Median age is approximately 50
- M:F ratio is 2:1

Blue – Japan; Red – US Per 100,000 people
Mature T-/NK-cell Neoplasms

**Cutaneous**
- Mycosis Fungoides (MF)
- Transformed MF
- Sézary Syndrome
- Primary Cutaneous CD30+ T-cell Disorders
- Primary Cutaneous Gamma/Delta TCL

**Extranodal**
- NK/TCL: Nasal Type
- Enteropathy-associated TCL
- Hepatosplenic TCL
- Subcutaneous Panniculitis-like TCL

**Nodal**
- Peripheral TCL-NOS
- Anaplastic Large Cell Lymphoma (ALK+/-)
- Angioimmunoblastic TCL

**Leukemic**
- Adult T-cell Leukemia/Lymphoma
- Aggressive NK-Cell Leukemia
- T-cell Prolymphocytic Leukemia
- T-cell Large Granular Lymphocytic Leukemia

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*Figure 1 (adapted from Rodriguez J, et al. Crit Rev Oncol Hematol. 2008)*
My estimation of INCIDENCE of extra nodal NK-T lymphoma

Approximately **10 million** people reside in LA County

Assuming **low estimate** of .04 incident cases / 100,000 would equal **4 new cases a year**

Assuming **high estimate** of .38 incident cases / 100,000 would equal **38 new cases a year**

Population of Oregon = 4 million, thus 2 cases per year would be significant in terms of incidence and expected given general US estimate
Epstein Barr Virus

- Tropism for B cells and epithelial cells
- Binds to CD 21 on B cells and B integrins on epithelial cells
- Transmitted by saliva
- Double stranded DNA virus

50% of 5 year olds in US infected
45% more will be infected by adulthood
(about 1/3 of these infected as adult will experience mono)

=95% of people in US show evidence of infection by adulthood

Virtually all cases of ENKL contain monoclonal episomal EBV DNA and detectable EBV encoded small nuclear RNAs (EBERs)
Natural Killer Cells Phenotype

Positive Markers
CD2 – NK/T cell marker
CD3 epsilon – cytoplasmic
CD56 – useful but not specific
Perforin, Granzyme B and TIA-1 (Cytotoxic molecules)

Negative Markers
Surface CD3
CD4, CD5, CD7, CD8
CD21

T-cell Genes
Germ-line T-cell receptor gene rearrangement supports NK phenotype
Clonal gene rearrangement suggests a cytotoxic T lymphocyte phenotype

Raymond Liang
Advances in the management and monitoring of extranodal NK/T-cell lymphoma, nasal type
2009 Blackwell Publishing Ltd, British Journal of Haematology, 147, 13–21
Pleomorphic cellular infiltrate. The cell size tends to be quite variable. With very few exceptions, angiocentricity is usually a prominent feature.
Extranodal NK/T Cell Lymphoma

Staging
Ann Arbor stage has been shown to be a significant factor for survival in patients with early-stage nasal NTCL.

(5-year OS, 42–78% for stage I and 19–46% for stage II).
Prognostic Systems

1) NK Cell Lymphoma Prognostic Index (Lee, et. al.)
Ann Arbor stage
LDH
B symptoms
Regional lymphadenopathy

2) International Prognostic Index

Score 1 for each factor present:
Age > 60 years
Serum LDH > normal
Performance status > 1
Stage III/IV
Extranodal site > 1

Final IPI risk group
0 or 1, low risk;
2, low-intermediate risk;
3, high-intermediate risk;
4 or 5, high risk

LDH, lactate dehydrogenase.

Table I. Prognostic factors in extranodal NK/T-cell lymphoma.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% CR</th>
<th>Median survival months</th>
<th>% 5y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>50-61</td>
<td>NR</td>
<td>36-39</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>44-64</td>
<td>NR</td>
<td>33-73</td>
</tr>
<tr>
<td>Ann Arbor stage III/IV*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>50-86</td>
<td>NR</td>
<td>42-78</td>
</tr>
<tr>
<td>II</td>
<td>46-86</td>
<td>NR</td>
<td>19-48</td>
</tr>
<tr>
<td>III/IV</td>
<td>23-42</td>
<td>NR</td>
<td>20</td>
</tr>
<tr>
<td>B symptoms*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>38-63</td>
<td>NR</td>
<td>19-33</td>
</tr>
<tr>
<td>Absent</td>
<td>60-75</td>
<td>NR</td>
<td>41-49</td>
</tr>
<tr>
<td>International Prognostic Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0-1)</td>
<td>58-92</td>
<td>&gt;10y</td>
<td>57.4 (20y)</td>
</tr>
<tr>
<td>Low intermediate (2)</td>
<td></td>
<td></td>
<td>27.6 (20y)</td>
</tr>
<tr>
<td>Nasal only</td>
<td>50-91</td>
<td></td>
<td>82 (8y)</td>
</tr>
<tr>
<td>High intermediate (3)</td>
<td></td>
<td></td>
<td>27.6 (20y)</td>
</tr>
<tr>
<td>Nasal only</td>
<td>14-92</td>
<td></td>
<td>90 (8y)</td>
</tr>
<tr>
<td>High (&gt;3)</td>
<td>5-90</td>
<td></td>
<td>84 (8y)</td>
</tr>
<tr>
<td>NK Lymphoma Prognostic Index*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0)</td>
<td>NR</td>
<td>&gt;10y</td>
<td>80.9</td>
</tr>
<tr>
<td>Low intermediate (1)</td>
<td></td>
<td></td>
<td>64.2</td>
</tr>
<tr>
<td>Intermediate high (2)</td>
<td></td>
<td></td>
<td>34.4</td>
</tr>
<tr>
<td>High (3-4)</td>
<td>NR</td>
<td>4-6</td>
<td>27.6 (20y)</td>
</tr>
<tr>
<td>EBV viral load at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6.1 x 10^7 copies/mL</td>
<td>NR</td>
<td>&gt;54</td>
<td>80.9</td>
</tr>
<tr>
<td>≥6.1 x 10^7 copies/mL</td>
<td>NR</td>
<td>2.1</td>
<td>64.2</td>
</tr>
</tbody>
</table>

NR, not reported; y, year; CR, complete remission; OS, overall survival.

*Risk factors contribute to the final IPI score.

Risk factors consist of the NK cell lymphoma prognostic index proposed by Lee, et al, including Ann Arbor stage, LDH, B symptoms, regional lymphadenopathy [24].
Survival according to the new prognostic index.

Group 1, n = 60 (27%); group 2, n = 68 (31%); group 3, n = 44 (20%); group 4, n = 47 (22%). OS, overall survival.

Survival according to IPI.

Low risk, n = 148 (69%); low-intermediate risk, n = 34 (16%); high-intermediate risk, n = 19 (9%); high risk, n = 14 (7%). OS, overall survival.
Natural Killer Cell Lymphomas

Timur Mitin and Karen M. Winkfield*
Department of Radiation Oncology, Massachusetts General Hospital Cancer Center, Boston, MA

<table>
<thead>
<tr>
<th>Table 2</th>
<th>International Prognostic Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factors</td>
<td>No. of Risk Factors</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>0 to 1</td>
</tr>
<tr>
<td>Serum LDH &gt;1X</td>
<td>2</td>
</tr>
<tr>
<td>PS 2-4</td>
<td>3</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>4 to 5</td>
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<tr>
<td>Extramedullary involvement &gt;1 site</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Korean Prognostic Index</th>
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</thead>
<tbody>
<tr>
<td>Risk Factors</td>
<td>No. of Factors</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>0</td>
</tr>
<tr>
<td>Serum LDH &gt;1X normal</td>
<td>1</td>
</tr>
<tr>
<td>Regional lymph node involvement</td>
<td>2</td>
</tr>
<tr>
<td>Ann Arbor Stage III/IV</td>
<td>3-4</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Japanese Prognostic Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factors</td>
<td>No. of Factors</td>
</tr>
<tr>
<td>Non-maligtype</td>
<td>0</td>
</tr>
<tr>
<td>Stage</td>
<td>1</td>
</tr>
<tr>
<td>Performance status</td>
<td>2</td>
</tr>
<tr>
<td>Extramedullary involvement</td>
<td>3-4</td>
</tr>
</tbody>
</table>
In situ hybridization for Epstein Barr virus-encoded early RNAs (EBER) positivity in NK/T-cell lymphoma

PET may not detect morphologically occult marrow infiltration uncovered by ISH for EBER

Pretreatment studies:

**Labs**
- CBC w/ diff, chemistries with liver and renal function and electrolytes
- Lactate dehydrogenase (LDH)
- Hepatitis B virus, HIV, and uric acid
- Measurement of a pretreatment plasma EBV DNA by quantitative polymerase chain reaction, if available

**Imaging**
- PET
- Cardiac Ejection Fraction

**BM biopsy**
- EBER ISH if available

**Other tests**
- Fiberoptic nasopharyngoscopy

**Authors**
Kensei Tobinai, MD, PhD
Motoko Yamaguchi, MD, PhD (lead author of Japan Onc Group Studies of NK/T)
Extranodal NK/T Cell Lymphoma

Treatment

There have been no randomized trials comparing treatment regimens for extranodal NK/T cell lymphoma, nasal type
NCCN Treatment Guidelines

Suggested treatment regimens in alphabetical order

**Combination chemotherapy regimen (paclitaxel-based)**
- ApraMedRx (paclitaxel, methotrexate, and dexamethasone) (Reported as a second-line regimen.)
- SMILE (steroid [dexamethasone], methotrexate, ifosfamide, paclitaxel, and etoposide)

**Concurrent chemoradiation therapy (CCRT)**
- CCRT (radiation 50 Gy and 3 courses of DeVIC [dexamethasone, etoposide, ifosfamide, and carboplatin])
- CCRT (radiation 40 to 52.8 Gy and cisplatin) followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)

**Sequential chemoradiation**
- SMILE followed by RT 45-50.4 Gy
- VIPD followed by RT 45-50.4 Gy

**Radiotherapy alone**
- Recommended tumor dose is ≥50 Gy
  - Early or up-front RT had an essential role in improved OS and DFS in patients with localized extranodal NK/T-cell lymphoma, nasal type, in the upper aerodigestive tract.
  - Up-front RT may yield more benefits on survival in patients with stage I disease.
Treatment depends on staging, and will be presented by:

Localized disease – Stages I and II
Systemic disease – Stages III and IV

ENKTL is both chemosensitive and radiosensitive

Data dating back to the 1970s
RT monotherapy showed response rates of 70% to 80%
5-year failure-free survival of 50% to 60%
Chemotherapy alone tends to yield a lower FFS of 25% to 40%.
Post-RT relapses were salvaged with chemotherapy.

- Combination of RT and chemotherapy is the current accepted standard of care for patients who can tolerate systemic treatment.
- Monotherapy with RT is reserved for patients with advanced age or comorbidity.

The optimal dose, combination, and sequence of radiotherapy and chemotherapy is still undefined.
FIGURE 2 Dose-response curve for NK cell lymphoma. Local control probability as function of radiation dose in patients treated with radiotherapy alone. Horizontal lines indicate range of RT doses delivered; vertical lines represent 95% CI of local control probability.

Source: Adapted from Ref (17). Reproduced with permission by Elsevier.
Treatment of Local Disease Stage 1E and 2E

**Radiation Therapy**

- Treated with definitive RT of 50-54 Gy with 2-3cm margins +/- chemotherapy (Hansen and Roach Handbook, 2nd Ed.)

- Radiation Field
  - Nasal cavity
  - Nasopharynx
  - Gross tumor volume with a sufficient margin.

- Patients likely have better outcomes with sequential (after RT) or concurrent chemotherapy

**Chemotherapy**

- CHOP chemotherapy, commonly used in other lymphomas, largely ineffective
  - Partially due to the presence of P-Glycoprotein

- Acceptable treatment regimens:
  - **DeVIC** (dexamethasone, etoposide, ifosfamide, and carboplatin) alone
  - Combination of weekly **cisplatin followed by VIPD** (etoposide, ifosfamide, cisplatin, and dexamethasone).
Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract.

82 cases reviewed
RT was the only independent prognostic factor
RT prognostic for both OS and DFS at both the univariate and multivariate level.

≥54 Gy of RT as compared with that of <54 Gy
5-year OS 75.5% vs. 46.1%, \( p = 0.019 \)
5-year DFS 60.3% vs. 33.4%, \( p = 0.004 \)

Up-front RT vs. initial CT followed by early RT
5-year OS 90.0% vs. 48.9%, \( p = 0.012 \)
5-year DFS 78.7% vs. 39.9%, \( p = 0.021 \)

Caveats IBNLT:
Not randomized, different stages, with more patients receiving chemo-only having B symptoms

Mei-juan Huang, M.D, et. al. 2008
International Journal of Radiation Oncology, Biology and Physics
A comparison of radiation treatment plans using IMRT with helical tomotherapy and 3D conformal radiotherapy for nasal natural killer/T-cell lymphoma

N TOMITA, MD, T KODAIRA, MD, H TACHIBANA, MD, T NAKAMURA, MD, R NAKAHARA, MD, H INOKUCHI, MD, N MIZOGUCHI, MD and A TAKADA, MD

Department of Radiation Oncology, Aichi Cancer Center Hospital, Nagoya, 464-8681, Japan

IMRT with HT versus 3D-CRT in NNKTL

→ RTPs for 8 patients previously treated with a pilot comparison between the two modalities

→ Parameters of Target Coverage and Homogeneity for the PTV

→ Maximum and Mean doses for organs at risk (OARS)

→ CTV included GTV + 1.5cm and NP, palates, and nasal cavity

→ PTV with the CTV plus a 2mm margin with a total does of 50 Gy
Conclusions - IMRT and HT
- Improves Target Coverage
- Greater Dose Uniformity
- IMRT potentially allows for higher doses (some studies report 54 Gy is needed to obtain in-field control)

“We believe insufficient target coverage and homogeneity within of 3D CRT might be largely due to the presence of the many OARs...anatomical complexity...that the application of these conventional 3D-CRT techniques might have caused local failure in previous studies.”
Chemotherapy and RT were simultaneously started within 7 days after registration.

The drug doses of level 1 (two thirds DeVIC) and the drug administration schedule were as follows:
- dexamethasone, 40 mg/d intravenously on days 1 to 3;
- etoposide, 67 mg/m2 intravenously over 2 hours on days 1 to 3;
- ifosfamide, 1.0 g/m2 intravenously over 3 hours on days 1 to 3;
- carboplatin, 200 mg/m2 intravenously over 30 minutes on day 1.

Radiation Therapy
50 Gy in 25 fractions over 5 weeks for stage IE disease
50.4 Gy in 28 fractions over 6 weeks for stage IIE disease.

All patients were treated with a photon beam of 4MV or greater.

Three dimensional conformal treatment planning was recommended, but not mandatory. Tissue heterogeneity correction was not used in dose calculations.

Clinical target volume (CTV) included gross tumor volume with a margin of at least 20 Mm and the entire nasal cavity and paranasal sinuses. Planning target volume (PTV) included CTV with a 5 mm margin. For stage IIE disease, CTV and PTV also included the involved cervical lymph node area. Use of a mouth spacer and two-step cone down of RT were recommended to reduce local toxicity.
2-year OS (79%); (95% CI, 57% to 89%) was superior to the historical control (45%). Based on these results and the excellent PTV control rate at 2 years (96%), we consider RT-2/3 DeVIC to be more effective than RT alone for the treatment of localized nasal NKTCL.

The incidence of mucositis in this study was 30%, which was lower than reported for concurrent chemoradiotherapy for head and neck cancer (38% to 57%). Use of a mouth spacer and two-step conedown of RT were considered to be important, resulting acceptable local toxicities of this study.
JCOG0211 UPDATE - Updated as of December 2011 for 5 year outcomes.

Could not identify risk factors at diagnosis predictive of OS or PFS in subgroup analyses of the current trial.

Monitoring EBV DNA load in peripheral blood might be useful for identification of risk factors for survival in patients treated with RT-2/3DeVIC

The OS at 5 years was 70% (95% CI, 49% to 84%; Fig 1A). Superior to the historical control of RT alone (40%)

The PFS at 5 years was 63% (95% CI, 42% to 78%; Fig 1B).

Recurrence within the RT field was observed in only two patients. Thus, the planning target-volume control rate at 5 years was 94% (31 of 33 patients).

Remember - The RT prescription
50 Gy in 25 fractions over 5 weeks for stage IE disease
50.4 Gy in 28 fractions over 6 weeks for stage IIE disease.
Is concurrent really better than sequential RT?

- Other retrospective studies have shown no benefit to concurrent vs sequential RT
- In fact in this study by Lee et al. RT was after CT and found no difference
- The 3-year OS rate of all patients was 66%

Limitations:
Different population (where incidence is 0.38 cases per 100,000)
Retrospective
The radiation doses differed
  median SCRT 54 Gy (range, 44-61.2 Gy)
  median CCRT 45 Gy (range, 44 –54 Gy)
Fig. 1  
Comparison of **progression-free survival** between patients treated with sequential chemotherapy followed by radiotherapy (SCRT, dotted line) and those treated with concurrent chemoradiotherapy (CCRT, solid line) (**P=0.823**).

Fig. 2  
Comparison of **overall survival** between patients treated with sequential chemotherapy followed by radiotherapy (SCRT, dotted line) and those treated with concurrent chemoradiotherapy (CCRT, solid line) (**P=0.670**).
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Stage IE</th>
<th>Stage IIE</th>
<th>CR (%)</th>
<th>OR (%)</th>
<th>Local/systemic relapse</th>
<th>Main toxicity</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamaguchi et al. (64)</td>
<td>RT: 50 Gy for Stage IE, 50.4 Gy for Stage IIE; CT: 3 courses of DeVIC</td>
<td>27</td>
<td>18</td>
<td>9</td>
<td>77</td>
<td>81</td>
<td>4%/33%</td>
<td>Mucositis</td>
<td>78% at 2 years</td>
</tr>
<tr>
<td>Kim et al. (75)</td>
<td>RT median 40 Gy; CT: weekly cisplatin 30 mg/m² with RT, then 3 courses of VIPD</td>
<td>30</td>
<td>15</td>
<td>15</td>
<td>80</td>
<td>83</td>
<td>7%/17%</td>
<td>Leucopenia</td>
<td>86% at 3 years</td>
</tr>
</tbody>
</table>

DeVIC: Dexamethasone 40 mg D1-3, etoposide 67 mg/m² D1-3, ifosfamide 1 g/m² D1-3, carboplatin 200 mg/m² D1 (q3 wks)
VIPD: Etoposide 160 mg/m² D1-3, ifosfamide 1.2 g/m² D1-3, cisplatin 33 mg/m² D1-3, dexamethasone 40 mg D1-4 (q3 wks)
Treatment of Local Disease Stage 1E and 2E SUMMARY

- For patients with localized extranodal NK/T cell lymphoma, nasal type, **RT is indicated**, whether before or concurrently with chemo if pt can tolerate chemo.

- Radiation Dose of 50, ideally 54Gy when preceding chemo. Radiation Dose of 50 Gy and concurrent therapy with two-thirds dose DeVIC alone or RT of 40 Gy with weekly cisplatin followed by VIPD.
The best treatment option for patients with disseminated (stage III or IV) is unknown.

Patients should be encouraged to participate in clinical trials whenever possible.

Only approximately 30 percent of such patients will achieve a complete remission with anthracycline-based chemotherapy, median survival with chemotherapy is approximately 4.3 months.

Several regimens incorporating L-asparaginase as salvage therapy have shown promising results.

Multicenter phase II study of L-asparaginase, methotrexate, and dexamethasone (AspaMetDex) in 19 patients with relapsed or refractory disease reported an ORR of 78% (61 %CR).

Patients that had a complete response (CR) showed better prognosis when undergoing HSCT than those who received HSCT during non CR, therefore, better chemotherapy is imperative for outcomes in regards to HSCT.
**SMILE Phase 2**

International Workshop Criteria (IWC) for assessing response to treatment in non-Hodgkin lymphoma (NHL)

<table>
<thead>
<tr>
<th>Complete remission (CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No clinical evidence of disease or disease-related symptoms.</td>
</tr>
<tr>
<td>• Typically FDG-avid lymphomas: a post-treatment residual mass of any size is permitted as long as it is PET negative.</td>
</tr>
<tr>
<td>• Variable FDG-avid lymphoma/FGD avidity unknown: all lymph nodes normal size by CT.</td>
</tr>
<tr>
<td>Spleen and liver non-palpable and without nodules.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Partial remission (PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression of measurable disease with at least 50 percent decrease in nodal size as determined by SPD.</td>
</tr>
<tr>
<td>For a typically FDG-avid lymphoma, the post-treatment PET should be positive in at least one previously involved site.</td>
</tr>
<tr>
<td>No increase in the size of other nodes, liver, or spleen.</td>
</tr>
<tr>
<td>Regression of splenic or hepatic nodules by at least 50 percent as determined by the SPD.</td>
</tr>
<tr>
<td>No new sites of disease.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stable disease (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to attain CR/PR or PD.</td>
</tr>
<tr>
<td>For typically FDG-avid lymphomas, the post-treatment PET should be positive at prior sites of disease and no new sites should be present on PET or CT.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relapse after CR or Progressive disease (PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance of any new lesion more than 1.5 cm in long axis. If long axis is 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0 cm.</td>
</tr>
<tr>
<td>50 percent increase in the largest diameter of a previously identified node more than 1 cm in short axis or in the SPD of more than one node.</td>
</tr>
<tr>
<td>Lesions &gt;1.5 cm should be PET positive in typical FDG-avid lymphoma or if PET positive before therapy.</td>
</tr>
<tr>
<td>Increasing FDG uptake in a previously unaffected site should only be considered relapse or PD after confirmation with other modalities.</td>
</tr>
<tr>
<td>New or recurrent involvement of the bone marrow.</td>
</tr>
</tbody>
</table>

Typically FDG-avid lymphomas include: diffuse large B cell lymphoma, Hodgkin lymphoma, follicular lymphoma, and mantle cell lymphoma. Variable FDG-avid lymphomas include all other non-Hodgkin lymphomas.

SMILE Phase 2

Fig 1. Kaplan-Meier estimates of overall survival (OS) of patients treated with steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide chemotherapy.

(A) The 1-year OS of 38 patients was 55% (95% CI, 38% to 69%).

(B) The 1-year OS was 82% (95% CI, 55% to 94%) for patients who attained complete response (CR) and 54% (95% CI, 25% to 76%) for those who attained partial response (PR).

At a median follow-up of 24 months, progression-free and overall survival rates at one year were 53 and 55 percent, respectively.

Full-dose administration of SMILE should be avoided for patients who are in poor condition -including those with lymphopenia less than 500/L -or large tumor burden.
**SMILE Phase 2**

**KM estimates of OS and PFS by subgroup (n=38)**

A) 45% for newly diagnosed vs 79% relapsed (p=.04)

B) 45% for newly diagnosed vs 71% relapsed (p=.05)

“Our results indicate that SMILE chemotherapy is effective for the treatment of newly diagnosed stage IV, relapsed, or refractory ENKL. The ORR after two cycles of SMILE (79%; 90% CI, 65% to 89%) clearly exceeded the threshold ORR (35%). The 1-year OS rate (55%) was much improved compared with the previous treatment strategy. Patients who proceeded with autologous HSCT had a trend towards increased survival that did not reach statistical significance.”
Assessing Response To Treatment

Response assessment — One month following the completion of planned therapy (or sooner if the outcome is unfavorable), the response to treatment should be documented by:

- History
- Physical examination
- Flexible nasal endoscopic examination - during the flexible nasal endoscopy, biopsies should be taken of any suspicious lesions and of random normal looking mucosa
- Laboratory studies (complete blood count, lactate dehydrogenase, biochemical profile, and plasma EBV DNA by quantitative polymerase chain reaction, if available)
- The post-treatment imaging study of choice is the PET/CT scan, which provides information on the size and activity of residual masses and allows for the distinction between active disease and fibrosis.
- PET/CT should be obtained six to eight weeks after completion of chemotherapy and 12 weeks after the completion of radiation therapy.

Authors
Kensei Tobinai, MD, PhD
Motoko Yamaguchi, MD, PhD (lead author of Japan Onc Group Studies of NK/T including SMILE)
Extranodal NK/T Cell Lymphoma

EBV TITERS
Mechanism of detection of fragmented EBV-DNA in peripheral blood. Episomal EBV-DNA exists in lymphoma cells. In the process of tumor growth some lymphoma cells are induced to apoptosis. Cell-free fragments of EBV-DNA, as well as human DNA, are released from the apoptotic lymphoma cells, and are leaked into peripheral blood.
Clinical implications of plasma Epstein-Barr virus DNA in early-stage extranodal nasal-type NK/T-cell lymphoma patients receiving primary radiotherapy

by Zhao-Yang Wang et. al.

Comparison of patients with detectable vs undetectable EBV-DNA after treatment

The 3-year OS and PFS rates were 92.0% and 77.5%, respectively, for patients with undetectable EBV-DNA levels after treatment

Compared with 69.8% (P=0.028) and 50.7% (P=0.031) for those with detectable levels of EBV-DNA after treatment

Blood
Volume 120(10):2003-2010
September 6, 2012
Correlations.


Comparisons by stage.

The pretreatment EBV-DNA concentrations for patients with B-symptoms, elevated LDH, or IPI score of 1-2 were significantly higher than those without B-symptoms (P < .002) or with a normal LDH level (P < .003) and an IPI score of 0 (P < .019; Figure 1).

The median concentration of EBV-DNA in all patients was 0 copies/mL after treatment (vs 491 copies/mL pretreatment; P < .003). The median concentration of EBV-DNA for the stage I patients was 314 copies/mL pretreatment, which decreased to 0 copies/mL after treatment (P < .001).

Survival.

(A) OS according to EBV titer and (B) PFS according to EBV titer.

The prognostic value of EBV-DNA was evaluated in patients with stage I and II disease. For patients with a pretreatment EBV-DNA concentration of 500 copies/mL (n = 35), the 3-year OS and PFS rates were 97.1%, and 79.0%, respectively 66.3% (P<0.002) and 52.2% (P<0.045) in patients with a pretreatment EBV-DNA concentration of 500 copies/mL.
Prospective measurement of Epstein-Barr virus-DNA in plasma and peripheral blood mononuclear cells of extranodal NK/T-cell lymphoma, nasal type

**Table 3. Prognostic factors affecting overall survival**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unfavorable factors</th>
<th>Hazard ratio (CI)</th>
<th>P</th>
<th>Hazard ratio (CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;50 years</td>
<td>0.5 (0.2-1.9)</td>
<td>0.33</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LDH level</td>
<td>Elevated</td>
<td>8.6 (2.4-30.4)</td>
<td>0.001</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>B symptom</td>
<td>Present</td>
<td>5.0 (1.3-19.0)</td>
<td>0.02</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>WB EBV-DNA</td>
<td>≥10⁶ copies/mL</td>
<td>53.2 (5.9-482.0)</td>
<td>&lt;0.001</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Plasma EBV-DNA</td>
<td>≥10⁴ copies/mL</td>
<td>10.3 (2.9-36.3)</td>
<td>0.001</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>EBER</td>
<td>&gt;75%</td>
<td>4.0 (1.2-13.7)</td>
<td>0.03</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Final model.

**Table 2. Correlation of the levels of EBV-DNA and response/adverse events to SMILE chemotherapy for newly diagnosed stage IV, relapsed or refractory ENKL**

<table>
<thead>
<tr>
<th>Response</th>
<th>Whole blood EBV-DNA</th>
<th>Plasma EBV-DNA (copies/mL)</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;10⁶ copies/mL</td>
<td>&lt;5×10⁵ copies/mL</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>11</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>8</td>
<td>0.005</td>
<td>0.002</td>
</tr>
<tr>
<td>NR</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ED</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Adverse event</td>
<td>Any grade 4ª</td>
<td>5</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No grade 4</td>
<td>0</td>
<td>1</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; ED, early death; PD, progressive disease; PR, partial response; NR, No response.

ªGrade 4 adverse events other than leukopenia and neutropenia.
Case Report
Staging
STAGE IV (per notes and PET) or STAGE III S (per BMB)

1. Upper nasopharynx with extension involving the bilateral adenoids and bilateral palatine tonsils. This mass measures approximately $8 \times 5.1 \text{ cm}$ in size in the transverse and AP dimensions respectively. This mass is causing narrowing of the adjacent airway. Bilateral, pathologically enlarged level II and III lymph nodes are identified with increased metabolic activity. The largest approximately 1.2 cm with increased SUV.

2. Increased activity and enlargement of the spleen consistent with lymphomatous involvement.

3. Mild, however, increased metabolic activity in the axial and appendicular skeleton worrisome for lymphomatous involvement.

PERIPHERAL BLOOD: Normochromic, normocytic anemia, moderate. Leukopenia, mild.

Bone Marrow Biopsy:
BONE MARROW ASPIRATION, TREPHINE BIOPSY IMPRINTS AND TREPHINE BIOPSIES:

Normocellular bone marrow (60%) with no evidence of involvement by lymphoma. History of extranodal NK T-cell lymphoma, nasal type.
IMPRESSION: 1. Extensive mass in the nasopharynx with increased metabolic activity consistent with reported history of NT-cell lymphoma. There is also involvement of bilateral cervical nodes, as described above.
2. Increased activity and enlargement of the spleen consistent with lymphomatous involvement. 3. Mild, however, increased metabolic activity in the axial and appendicular skeleton worrisome for lymphomatous involvement. Please note that the mass in the nasopharynx is causing narrowing of the airway.
Case Report
Treatment and Outcome
Treatment and Course

• Pt initial eval by Rad Onc on 04/10/12 right around time of diagnosis
  Note advises considering SMILE and EBV titer, appointment with Heme/Onc with request to see patient again after chemo for re-evaluation

• Pt underwent four cycles of SMILE 04/18/12 - 07/18/12

• Follow Up PET scans, with no e/o uptake, pt showing CR (images to follow)

• Seen again by Rad Onc on 5/30/12: In setting of stage IV disease and CR, do not recommend consolidative XRT to the primary site. Then co-followed by HEME and ENT

• 12/4/12 Polypoid lesion at ENT appointment, followed until biopsy 03/03/2014
  3/25/14 Final Pathologic Diagnosis: (A): Right nasopharyngeal mass, biopsy: Extranodal NK/T-cell lymphoma, nasal type

• 06/2014 referred to Rad Onc and patient was seen for consult and currently on treatment with RT with the plan in following slides
4/17/12 vs 4/23/13 Fused PET CT scans
Treatment and Course (cont’d)
Treatment and Course (cont’d)
Ideal treatment of patients with Stage III and IV disease is still unknown as described before.

This case presents several questions that we do not have answers for. A multicenter RCT will be required to begin to answer them.

1) When this patient was thought to be in CR based on PET scans, would an EBV titer have shown evidence that the patient in fact had residual disease?

2) But then, what course should one pursue in this patient if he has a rising titer but no clinical or PET evidence of disease?

3) Given the current plan is for RT for this patient to a full dose of 50Gy, is there a role for initial RT before smile, sandwiched RT, or consolidative RT after smile? Or is it best to reserve RT as an intervention for recurrence?

4) Does the patient qualifying vs. not qualifying for HSCT impact this decision?
Extranodal NK/T Cell Lymphoma

Thanks to everyone in the OHSU Department of Radiation Oncology for the opportunity to rotate!

Comments...

Questions?