Meta-Analysis in Lymphomas

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Questions answered by meta-analysis in contemporary management of lymphomas

- PET in Systemic Lymphomas
  - Staging (diagnostic performance of bone marrow involvement)
  - Response assessment

- PET in Primary CNS Lymphomas

- Role of Immunochemotherapy in Lymphomas
  - Rituximab in DLBCL

- Role of consolidation RT in Lymphomas in rituximab era
  - Hodgkin Lymphomas
  - Non-Hodgkin Lymphomas

- Role of Radiation therapy in NK T cell Lymphomas

PET in Hodgkin Lymphomas
- Staging (diagnostic performance of bone marrow involvement)

Systematic review and meta-analysis on the diagnostic performance of FDG-PET/CT in detecting bone marrow involvement in newly diagnosed Hodgkin lymphoma: Is bone marrow biopsy still necessary?

- N= 9 eligible studies
- N=955 pts
- Moderate methodological quality using QUADAS-2 scores
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PET in Hodgkin Lymphomas:
- Staging (diagnostic performance for bone marrow involvement)

- Pooled Sensitivity: 96.9% [95% CI 93.0% to 99.0%]
- Pooled Specificity: 99.7% (95% CI 98.9% to 100%)
- The area under the ROC curve was 0.9860.
- The proportion of FDG PET/CT-negative patients with a positive BMB among all cases was 1.1% (95% CI 0.6% to 2.0%).

PET in DLBCL Lymphomas:
- Staging (diagnostic performance for bone marrow involvement)

- N= Seven studies, with a total of 654 pts
- Pooled Sensitivity: 88.7% (95% CI, 82.5–93.3%)
- Pooled Specificity: 99.8% (95% CI 98.8 – 100%)
- The area under the sROC curve was 0.9983.
- Proportion of PET/CT-negative patients with positive BMB findings was 3.1%.
- Proportion of PET/CT-positive patients with negative BMB findings was 12.5%.

PET in Systemic Lymphomas: Response assessment

Predictive Value of Interim PET/CT in DLBCL Treated with R-CHOP: Meta-Analysis

Systematic review and meta-analysis on the prognostic value of complete remission status at interim PET/CT in DLBCL from the 12 included studies reveals a significant association with event-free survival. The area under the ROC curve was 0.9516 (95% CI 0.926–0.977).
PET in Systemic Lymphomas: Diagnostic performance of Interim PET

N=10 STUDIES
- Sensitivity, specificity, positive predictive value and negative predictive value of interim FDG-PET for predicting treatment failure.
- Pooled sensitivity: 70.8% (95% CI: 64%-77%)
- Pooled specificity: 89.9% (95% CI: 88.0–91.6%)
- PPV: 86.0%
- NPV: 98.6%

Take Home message:
- The overall prognostic value of interim PET is moderate for excluding and relatively high for identifying treatment failure in HL.
- Interim PET cannot yet be implemented in routine clinical practice due to moderate-quality evidence and inter-study heterogeneity that cannot be fully explained yet.

PET in Systemic Lymphomas: Role of Surveillance PET

N=15 STUDIES
- 7 DLBCL, 6 HL, and 2 HL and DLBCL
- N=3099 patients

Summary and recommendations:
- No survival advantage with the use of surveillance imaging for patients with DLBCL or HL who achieved remission after first-line therapy.
- Surveillance imaging produces additional radiation exposure.
- Recommend that patients with HL and DLBCL who achieve CR should not receive routine surveillance imaging (Lugano2014) - grade IB recommendation.
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PET scan in Primary CNS Lymphomas

- Pooled sensitivity in diagnosis: 0.88 (95% CI: 0.80–0.94)
- Pooled specificity in the diagnosis: 0.86 (95% CI: 0.73–0.94)
- Pooled positive likelihood ratio (PLR): 3.99 (95% CI: 2.31–6.90)
- Negative likelihood ratio (NLR): 0.11 (95% CI: 0.04–0.32)
- Pooled diagnostic odds ratio (DOR): 33.40 (95% CI: 10.40–107.3)

Take Home Message
- 18F-FDG PET and PET/CT are valuable radiological diagnostic tools in immunocompetent PCNSL patients.
- Complements MRI
- Helpful in narrowing down the differential diagnosis in pts suspected to have PCNSL.
- Based on the high diagnostic value of PET, can be recommended in routine clinical practice.
Role of consolidation therapy in Hodgkin lymphomas

Role of consolidation therapy versus combined modality treatment trials in Hodgkin’s disease. International Disease in Hodgkin’s Disease Overview Study Group.

- SCREENED 26 RANDOMIZED TRIALS
- TRIALS INCLUDED IN THE STUDY 9
- NO OF PATIENTS 570
- QUESTION ASKED: Role of consolidation RT in Hodgkin’s lymphoma
- End-points questioned:
  - overall survival
  - disease control
  - time-to-treatment related death

Role of consolidation therapy in Hodgkin lymphomas

Trials comparing addition of RT vs no RT
- No = 7 TRIALS
- N=918 PTS
- Conclusion
  - HR 0.51 - 11% benefit in the additional RT arms (p=0.01)
  - Multivariate analysis confirmed the results
  - HR reduced by 40%; relative risk 0.63 (95% CI: 0.50 - 0.78)

Role of consolidation therapy in Hodgkin lymphomas

Trials comparing addition of RT vs addition of CT
- No = 7 TRIALS
- N=837 PTS
- Conclusion
  - No improvement in overall survival by addition of CT after primary chemotherapy (p=0.43)
  - Multivariate analysis
    - RR 1.07 (95% CI: 0.85 - 1.34)
Role of consolidation therapy in Hodgkin lymphomas: cumulative incidence of leukemia

Caveats
- Radiation doses were high: 40-50Gy
- Large volumes were treated: EFRT was commonly employed
- Contemporary era: radiation doses have been deescalated to 20-30Gy

Role of consolidation therapy in non-Hodgkin lymphomas

The Role of Consolidative Radiotherapy after a Complete Response to Chemotherapy in the Treatment of Diffuse Large B-Cell Lymphoma in the Rituximab Era: Results from a Systematic Review with a Meta-Analysis

Acta Hematologica, 2015

N= 4 studies
All retrospective studies
N= 633 pts
Question asked: Efficacy of consolidation RT after CR in DLBCL after R-CHOP therapy
End points studied: Overall survival and progression free survival
Role of Immunochemotherapy in Lymphomas

A systematic review and meta-analysis of immunochemotherapy with rituximab for B-cell non-Hodgkin’s lymphoma

Guanghui Gao, Xiaohua Liang, Jingwei Jiang, Xinli Zhou, Ruofan Huang, Zhaohui Chu & Qiong Zhan

Acta Oncologica, 2010

- No. 12 studies
- No. of patients
- Histology: diffuse large B-cell lymphomas & Follicular lymphomas, mantle cell lymphomas
- Efficacy of rituximab with CHOP or CHOP-like chemotherapies
- Endpoints: overall survival, overall response, disease control, and adverse events
Role of Immunochemotherapy in Lymphomas

<table>
<thead>
<tr>
<th>First author</th>
<th>Lymphoma subtype</th>
<th>Quality score</th>
<th>Study arms</th>
<th>Total patients</th>
<th>Eligible patients</th>
<th>Previous therapy</th>
<th>Stage</th>
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<tbody>
<tr>
<td>Coiffier et al.</td>
<td>DLBCL, 3</td>
<td>R-CHOP, CHOP</td>
<td>500</td>
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<tr>
<td>Campo et al.</td>
<td>FL, DLBCL, 3</td>
<td>R-CHOP, FCR</td>
<td>145</td>
<td>120</td>
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<td>Willemze et al.</td>
<td>FL, 3</td>
<td>R-CHOP, MOP</td>
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<td>Zinzani et al.</td>
<td>FL, 3</td>
<td>R-CHOP, MOP</td>
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<td>Caldara et al.</td>
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<td>Metallic et al.</td>
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<td>Overall survival among patients receiving rituximab with chemotherapy (R-chemo) or chemotherapy alone</td>
<td></td>
<td></td>
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</tbody>
</table>

Overall survival for the subgroups with diffuse large B-cell lymphoma, mantle cell lymphoma or follicular lymphoma receiving chemotherapy (R-chemo) or chemotherapy alone.
**Role of Immunochemotherapy in Lymphomas**

**Rituximab in Lymphomas**

<table>
<thead>
<tr>
<th>Study</th>
<th>Rituximab + Chemotherapy</th>
<th>Chemotherapy Alone</th>
<th>RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>0.85</td>
<td>0.75</td>
<td>1.12</td>
<td>0.05</td>
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<tr>
<td>Study 2</td>
<td>0.80</td>
<td>0.70</td>
<td>1.15</td>
<td>0.02</td>
</tr>
<tr>
<td>Study 3</td>
<td>0.75</td>
<td>0.65</td>
<td>1.17</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Meta-analysis of disease control for all patients receiving rituximab with chemotherapy (R-chemo) vs chemotherapy alone. Disease control is shown as the relative risks (RR) for a disease event (progression, relapse, death).

*Take Home Message:*
- Addition of Rituximab improves overall and progression-free survival in all lymphomas.
- It should be recommended in all CD20-positive lymphomas.

**Role of radiation therapy in the contemporary management of NK T cell Lymphomas**

**Meta Analysis of Treatment for Stage IE-IIE Extramedullary Natural Killer / T Cell Lymphomas in China**

<table>
<thead>
<tr>
<th>Study</th>
<th>No of Trials Included</th>
<th>No of Patients</th>
<th>Type of Studies</th>
<th>Subjects</th>
<th>Heterogeneity</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>11</td>
<td>871</td>
<td>Randomized Controlled Trials</td>
<td>Stage 6-46</td>
<td>I² = 0-55%</td>
<td>1. Sequencing of RT and chemotherapy 2. RT alone vs combined modality therapy 3. Combined modality therapy vs chemotherapy</td>
</tr>
</tbody>
</table>

**End points**
- Complete remission rates
- Overall survival

**Overall survival - combined therapy vs radiotherapy alone**

<table>
<thead>
<tr>
<th>Study</th>
<th>3 Years Survival</th>
<th>5 Years Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>0.85</td>
<td>0.70</td>
</tr>
<tr>
<td>Study 2</td>
<td>0.75</td>
<td>0.65</td>
</tr>
<tr>
<td>Study 3</td>
<td>0.65</td>
<td>0.55</td>
</tr>
</tbody>
</table>

2 RCT's compared 3 years survival and 6 RCT's compared 5 year survival rates.
Overall survival - combined therapy vs chemotherapy alone

No. of RCTs: 9-122 patients

Overall survival - timing of radiotherapy

No. of RCTs: 9-122 patients

The optimal timing of radiotherapy in the combined modality therapy for limited-stage extranodal NK/T cell lymphoma (ENKTL): a systematic review and meta-analysis

Annals of Hematology, 2018

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**Overall survival - Timing of radiotherapy**
- N=7 studies
- N=1489 pts
- \( I^2 = 0\% \)  
  \( (HR = 0.70, 95\% CI 0.55–0.88, P = 0.002) \)

**Progression-free survival - Timing of radiotherapy**
- N=4 studies
- N=454 pts
  \( HR = 0.72 \) in favor of upfront RT, 95%CI 0.43–1.19, P = 0.2
  \( (HR = 0.55, 95\% CI 0.37–0.80, P = 0.002) \)

**Complete remission rate - Timing of radiotherapy**
- N=5 Studies
- N=669 pts

There was no significant difference in CR rate between upfront RT and late RT  
\( (OR = 1.31 \) in favor of upfront RT, 95% CI 0.83 to 2.08; P = 0.25 \)
Meta-Analysis – NK T cell Lymphomas
(Take Home message)

- Upfront RT confers survival advantage over late RT in the combined modality therapy.
- Upfront RT may not have any advantage in complete response rates over late RT in the combined modality.
- Combination therapy has better clinical outcomes as compared to single modality (RT or chemotherapy alone)

Thank you!