Current Perspectives in Diffuse Large B-Cell Lymphoma

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Overview
- Background
- Epidemiology
- Diagnosis and Staging
- Current Therapy
- CHOP to R-CHOP
- Areas of unmet need
- Adverse prognostic features
- Research

BACKGROUND

Epidemiology
- Approx. 4800 new cases/year (CRUK data)
- This is around 50% of all NHL diagnoses
- Slight male preponderance (52:48)
- Primarily a disease of older age (median 59) with only 9% of cases occurring <45 years

Aetiology
- The incidence is increasing over time
- Most aetiologic factors unclear but include:
  - Infection (Hep, HIV [18x risk], EBV)
  - Ionising radiation
  - Immunosuppression- post-transplant lymphoproliferative disorders, 8x risk

DIAGNOSIS AND STAGING
Diagnosis of Lymphoma
- History
  - Include B symptoms
  - Seek evidence of occult disease: organ dysfunction, recurrent infections
- Clinical Exam
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Biopsy of a representative mass: histopathology
  - Excision preferred, else incision/core
  - DO NOT do FNA!
- Staging
  - Extent of disease

Histopathology
- Must be a good biopsy!
- Tissue NOT cells
- Morphology
- Immunohistochemistry (IHC)
- Cell surface markers
  - CD20, 10, 30, 15, 5, 4, 8, 3 etc
- Molecular tests
  - Fluorescent In Situ Hybridisation
  - Polymerase Chain Reaction
  - Gene Expression Profiling

Histological Appearances
- DLBCL
- Follicular Lymphoma

Staging Investigations
- CT scan (thorax, abdomen, pelvis, neck)
- PET
- Bone marrow biopsy - usually trephine only
- FBC & ESR
- Biochemical profile (inc LDH)
- Lumbar puncture (if high risk/peri-neuroaxis/testis)

CT Staging
- Ann Arbor formalised this into Stages 1-4, A + B
- The Cotswold Modification introduced:
  - X for bulk
  - E for Extramedullary
  - CR(u)

DLBCL: Retroperitoneal Mass

PET Staging
- Changes stage in up to 30% of patients
- Changes therapy in fewer...
- Has not (yet) demonstrated improvement in outcome
- May be able to replace BM biopsy in selected lymphoma histiotype

DLBCL: Widespread Abdominal Disease

The Lugano Classification

20/04/2017
Main Themes

- Simplifying stage overall
- Extending the use of PET:
  - To iNHL
  - Interim!
- Integrating Deauville and formally defining 'PET negative'
- Assessment of BM involvement rather than biopsy
- Deprecating CT and B symptoms

Pulling Things Together

CURRENT THERAPY

Discovery of Chemotherapy

- 1950
  - Lymphoma treated with mustard, a derivative of mustard gas
- 1950’s
  - Methotrexate, vincristine, 6-MP and others discovered
- 1965
  - Combination chemotherapy is found to be more effective at treating lymphoma and leukaemia
  - Chemotherapy regimens introduced

Development of Chemotherapy Regimens

- MOPP
  - Late ‘60s
  - Effective but quite toxic
- CHOP
  - Early ’70s
  - Very effective in the non-Hodgkin lymphomas
  - Superseded more toxic combinations such as MOPP
- ABVD
  - Designed in Italy in the late ’70s
  - Still a ‘gold standard’ treatment for Hodgkin Lymphoma to this day
  - Will cure >90% of early≥70% of late stage disease

Rituximab

- R-CHOP
  - Rituximab initially developed in 1986
  - Undergoes clinical trials in the 1990’s
  - CHOP vs R-CHOP
  - GELA- advanced stage, elderly
  - MiNT- advanced stage, younger
  - FDA approved in 1997
  - NICE approved in 2003

R-CHOP is the standard of care for DLBCL

- Intensified regimens not superior to CHOP in pre-Rituximab era and convincing randomised data favouring RCHOP as the standard of care for all ages and IPI scores
UNMET NEED

International Prognostic Index

- Age >60
- Stage 3 or 4 (or advanced)
- Lactate Dehydrogenase > ULN
- Performance Score >2
- Extramedullary Sites >1

- Each factor scores 1 point

International Prognostic Index

- Most studies have stratified risk and treatment outcome by IPI (or aaIPI)
- IPI remains a valid prognostic discriminator in the R-CHOP era
- But is this sensitive enough to evaluate novel strategies?

GELA ACVBP trials

R-ACVBP + consolidation schedule in LNH 03-2B R-CHOP vs DA-EPOCH-R + GCSF, n=78, 40% aaIPI 3-5 (abstract, JCO)

- Longer EFS, OS for ACVBP
- Fewer CNS relapses
- More toxic than CHOP

DA-EPOCH-R

- Rationale that PD driven dose adjustment overcomes adverse effects of tumour proliferation and BCL2

LNH 93-5

Phase III ACVBP vs CHOP in 61-69, aaIPI

- Longer EFS, OS for ACVBP
- Fewer CNS relapses
- More toxic than CHOP

Meta-analysis shows no benefit of ASCT in first-line treatment pre-rituximab

Meta-analysis of RCT performed on 2228 patients undergoing first-line ASCT for Aggressive NHL in the pre-rituximab era

DA-EPOCH-R – Rationale that PD driven dose adjustment overcomes adverse effects of tumour proliferation and BCL2

R-CHOP vs DA-EPOCH-R

- Phase II CALGB 50303: 6-8 cycles R-CHOP vs DA-EPOCH-R + GCSF, n=79, 40% IPI 3-5 (abstract, JCO)
- 90% achieved PD endpoint of grade 4 neutropenia
- ORR 100% (CR 68%, PR 32%)
- OS 88% at 18 months
- Phase II CALGB 50303 comparing RCHOP with DA-EPOCH-R showed no difference

REMöDL-B

- DLBCL can be stratified into (at least) 2 phenotypic subtypes by gene expression profiling (GEP)

- Germinal-centre B-cell (GCB)
- Activated B-cell (ABC)
**NEW AGENTS IN DLBCL**

**DLBCL- Treatment Failure**
- Approximately 40% of patients with DLBCL will ultimately relapse following 1st line R-CHOP
- This scenario was looked at in:
  - PARMA
  - CORAL

**Coral Results**
- In relapsing patients not previously treated with rituximab
  - ORR 82%
  - 2 yr EFS 66%
- In refractory patients (<12months) to upfront rituximab
  - ORR 54%
  - 2 yr EFS 34%

**Bortezomib**
- Enhances apoptosis via a complex pathway involving the proteosome and IFκB

**Remodl B Study Design**

**Salvage Regimens With Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era**
- R-ICE vs R-DHAP
- 1:1 randomisation
- 396 Pts in first relapse
- Only 50% Pts proceeded to autologous SCT
- Combined ORR 63% CR 38%
- 10% PBSCH failure in both arms
- 2nd randomisation to maintenance R made no difference to outcome

**Overall survival according to the first randomisation (ITT analysis)**

**Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin lymphoma**
- "Parma Study"

**PARMA**
- 2x DHAP then autologous Transplantation

**CORAL**
- 6x DHAP

**CORAL Results**
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Hallmarks of Cancer: The Next Generation

Cell Signalling

Small Molecule
- BTki
- Ibrutinib
- SYKi
- TAK659
- Entusapantinib
- mTOR, PI3K
- Idelalisib
- AZD2014
- Everolimus
- EZH2i
- E7438
- SINE
- Selinexor

Immunomodulators
- Lenalidomide
  - ORR ~50%
  - Mainly in ABC subtype
  - Synergistic with rituximab (R2)
- Checkpoint Inhibitors
  - Mainly PD1(L) axis
  - Nivolumab
  - Durvalumab
  - Avelumab

MAbs in lymphoma

Strategies for enhancing the potency of antitumour antibodies

Monoclonals
- Radioimmunotherapy
  - Zevalin already licensed
  - Anti-CD37 (Betalutin)
- Antibody-drug Conjugates
  - Brentuximab vedotin
  - Polatuzumab vedotin
  - ADCT-402

Others
- BiTE
  - Blinotumumab
  - Bind healthy T-cell (CD3) to malignant B-cell (CD19)
- Cellular Therapy / T-adoptive transfer
  - CAR-T 19
  - Genetically engineered T-cells vs malignant cells
Thank You

Any Questions?
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