The Lymphomas

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Overview

Lymphoma

– Where does it come from?
– How does it present?
– How is it diagnosed?
– How do we treat it?
– What is the outcome?
Where does it come from?

- Basically a malignant growth of white blood cells
- Predominantly in lymph nodes
- But also
  - Blood, bone marrow
  - Liver, spleen
  - Anywhere
Where does it come from?

- Primary immunodeficiency
  - Ataxia telangiectasia
  - Wiscott-Aldrich syndrome
  - Common variable immunodeficiency

- Secondary immunodeficiency
  - HIV
  - Transplant recipients

- Infection
  - EBV
  - HTLV-I
  - Helicobacter pylori

- Autoimmune disorders
How to patients present?

- Painless lump
- From other specialties
- B Symptoms
  - Night sweats
  - Weight loss
  - Itching
- Pain in nodal areas when drinking alcohol
  - Diagnostic of Hodgkin lymphoma
Diagnosis of lymphoma

- Blood film & bone marrow
- Lymph node biopsy
Diagnosis of lymphoma

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- Immunophenotyping
Diagnosis of lymphoma

- Blood film & bone marrow
- Lymph node biopsy
- Immunophenotyping
- Cytogenetics
bcl-2/IgH PCR in a series of bone marrow samples from patients with follicular centre lymphoma. A rearranged band is seen in lanes 2, 3, 4, 5, 8 & 9. Lane 11 is a standard. The varying size of the band illustrates the variation in breakpoints between patients.
Diagnosis of lymphoma

- Blood film & bone marrow
- Lymph node biopsy
- Immunophenotyping
- Cytogenetics
- Molecular techniques

i.e. diagnosis is complex

HODS
Lymphoma - Diagnosis

- Biopsy
  - Lymph node
  - Other tissue

- Staging investigations
  - Blood tests
  - CT Scan chest/abdo/pelvis
  - Bone marrow biopsy
Lymphoma - Diagnosis

And now …PET
What types of lymphoma are there?

Lots
WHO 2008 Classification – Mature B cell neoplasms

1. Chronic lymphocytic leukaemia/small lymphocytic lymphoma
2. B-cell prolymphocytic leukaemia
3. Splenic marginal zone lymphoma
4. Hairy cell leukaemia
   - Hairy cell leukemia-variant
5. Splenic lymphoma/leukemia, unclassifiable
6. Splenic diffuse red pulp small B-cell lymphoma
7. Lymphoplasmacytic lymphoma
8. Waldenström macroglobulinemia
9. Heavy chain diseases
   - Alpha heavy chain disease
   - Gamma heavy chain disease
   - Mu heavy chain disease
10. Plasma cell myeloma
11. Solitary plasmacytoma of bone
12. Extrasosseous plasmacytoma
13. Extrannodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
14. Nodal marginal zone B-cell lymphoma (MZL)
15. Pediatric type nodal MZL
16. Follicular lymphoma
   - Pediatric type follicular lymphoma
17. Primary cutaneous follicle center lymphoma
18. Mantle cell lymphoma
19. Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
   - T cell/histiocyte rich large B-cell lymphoma
   - DLBCL associated with chronic inflammation
   - Epstein-Barr virus (EBV)+ DLBCL of the elderly
20. Lymphomatoid granulomatosis
21. Primary mediastinal (thymic) large B-cell lymphoma
22. Intravascular large B-cell lymphoma
23. Primary cutaneous DLBCL, leg type
24. ALK+ large B-cell lymphoma
25. Plasmablastic lymphoma
26. Primary effusion lymphoma
27. Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
28. Burkitt lymphoma
29. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
30. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma
Broadly classify

- Hodgkin Lymphoma
- Non-Hodgkin lymphoma
  - B Cell
    - High Grade
    - Low Grade
  - T Cell (rare)
Hodgkin’s Lymphoma

Thomas Hodgkin described

‘Lymphogranulomatosis maligna’

in a paper entitled

‘On some morbid appearances of the absorbent glands and spleen’
Hodgkin’s Lymphoma

Presentation:
- Painless lymphadenopathy
- B symptoms
  - Sweats, weight loss
- Pain on alcohol consumption

Diagnosis: Reed-Sternberg cell
Numbers of new cases and age specific incidence rates, by sex, Hodgkin's lymphoma, UK 2003

Number of cases

Rate per 100,000 population

Age at diagnosis

Male cases
Female cases
Male rates
Female rates

Numbers of new cases and age specific incidence rates, by sex, Hodgkin's lymphoma, UK 2003
Hodgkin’s Lymphoma

- 4 clinical stages
- Anne Arbor
- B symptoms
  - Yes?
  - No?
Hodgkin’s - Treatment

Depends on clinical stage

- Early stage
  - Short course combination chemotherapy followed by radiotherapy
    - 70-80% prolonged disease free survival

- Advanced stage
  - Combination chemotherapy (ABVD)
    - 50-70% prolonged disease free survival

Relapse responds well to autologous bone marrow transplantation

Good long term survival – therefore must minimise long term effects of treatment
Hodgkin’s Lymphoma - Advances

- PET guided therapy
- If negative after 2 cycles
  - De-escalate chemotherapy
- If positive after 2 cycles
  - ?escalate treatment
  - Jury is out
Hodgkin’s Lymphoma - Advances

PET scan

2# ABVD

PET scan

PET +ve

Escalated BEACOPP

PET –ve

Randomise

4# ABVD v 4# AVD
Late Effects

- Happily ever after?
- E.g. infertility
- Anthracyclines –cardiomyopathy
- Bleomycin –lung damage
- Vinca alkaloids –peripheral neuropathy
- Second cancers
- Psychological issues
Non-Hodgkin’s Lymphoma
~ 4% of cancers & rising
Non Hodgkin’s Lymphoma

- Presentation
  - More varied

- Subtypes
  - More categories

- Treatments used
  - Wide variety

- Outcomes
  - More varied
Non Hodgkin’s Lymphoma

Low Grade
- eg Follicular NHL/Marginal zone/SLL
- Gradual onset
- Often asymptomatic
- Incurable ?functional cures
- Usually die of other things

Aggressive or High Grade
- eg Diffuse Large B Cell Lymphoma
- Short time course
- Usually symptomatic
- Potentially Curable
- Untreated leads to short life expectancy
Low grade NHL

- Slow growing
- Usually advanced at presentation
- Incurable
- Presents later in life (Median age 60)
- Median survival 9-11 years (improving)
- Wide range of treatments used
- Evolving therapy which is not traditional chemotherapy
Follicular lymphoma

- Commonest form for low grade lymphoma
- Often asymptomatic at diagnosis
- Usually present with advanced disease
- Treatment reserved for symptomatic disease
Tip of the iceberg
Treatment

- Watch and wait
- Early stage (1a)
  - Radiotherapy can be curative
  - Need to be sure is actually early stage
  - PET
- Chemotherapy-out patient regimens/gentle
- Rituximab maintenance
Treatment

- Relapse/remitting
- Remissions often several years/decades
- Only re-treat if becomes symptomatic again
- Majority of time spent in watch and wait
Indolent NHL - Outcome

Overall Survival (n = 4167)

Survival Probability

Time (months)
Transformation

- A significant cause of low grade mortality
- Lymphoma transforms into a high grade form
- Much more difficult to treat than usual high grade lymphoma
- Stem cell transplants required if fit
- Can get back to remission (just having low grade lymphoma)
The future

- Moving away from chemotherapy
- New drugs which target signalling pathways
  - Ibrutinib (BTK)
  - Idelalisib (Pi3K)
  - Venetoclax (BCL2)
  - Check point inhibitors (PD1)
High Grade lymphoma

- Diffuse large B Cell (DLBCL)
- Burkitt’s lymphoma
DLBCL

- Commonest form of high grade lymphoma
- Short onset (weeks/months)
- More likely to be symptomatic at diagnosis
- May be wide spread at diagnosis
- Can turn up in all sorts of places
  - Breast/kidneys/bones/CNS

[Image of CT scan showing pre-treatment and post-treatment comparison]
DLBCL Treatment

Early

- Short course chemotherapy + RT
- e.g. 3# R-CHOP & IFRT

Advanced

- Combination chemotherapy + monoclonal antibodies
- e.g. 6# R-CHOP
DLBCL Treatment outcomes

The graph illustrates the event-free survival probability over years after randomization for patients treated with CHOP plus rituximab and CHOP alone. The survival curves are significantly different, with a p-value of less than 0.001, indicating a statistically significant treatment effect favoring CHOP plus rituximab.
Newer Treatments/Approaches

- Increasing intensity of treatment
- Monoclonal antibodies
- Radioimmunoconjugates
Monoclonal antibodies

- Rituximab
- Monoclonal antibody
- Anti CD-20
- Targets CD20 expressed on cell surface of B-cells
- Chimeric mouse/human protein
- Minimal side-effects
\( ^{90} \text{Yttrium ibritumomab tiuxetan} \) (Zevalin)
CAR-T Cells

- Chimeric antigen receptor T-cells
- Taking patient’s T cells
- Programming them to attack cancer cells
Burkitt’s lymphoma

- Very high grade lymphoma
- Appears in days to weeks
- One of the fastest dividing malignancies known
- Often very sick
- Big abdominal masses/jaw mass
Burkitt’s lymphoma

- Associated with HIV
  - Endemic Burkitt’s
  - Related to EBV infection
- Particular cytogenetic abnormality - MYC
Treatment

- Multi-agent chemotherapy at very high doses (R-CODOX-M-R-IVAC)
- In patient regimen
- Tumour lysis syndrome—mass both grows and dies before your eyes
- Can show dramatic improvements in state of patient
Outcome

A. Overall survival

- age ≤60 and PS 0-1 (n=50)
- age >60 or PS >1 (n=45)
- age >60 and PS >1 (n=10)

P=0.000

Years

B. Disease-free survival

- age ≤60 and PS 0-1 (n=43)
- age >60 or PS >1 (n=33)
- age >60 and PS >1 (n=7)

P=0.0001

Years

C. Treatment-related mortality

- age >50 and PS >1 (n=10)
- age >50 or PS >1 (n=45)
- age ≤50 and PS 0-1 (n=50)

P=0.02

Years

D. Cumulative incidence of relapse

- age >60 and PS >1 (n=7)
- age >60 or PS >1 (n=33)
- age ≤60 or PS 0-1 (n=43)

P=0.05

Years
Conclusions

- Lymphoma encompasses a wide range of conditions
- Diagnosis and risk assessment becoming increasingly complex
- Range from very aggressive to indolent
- Variable prognosis
- Ever expanding range of treatments including designer drugs
- Tailoring treatment to improve outcomes
Questions?

I see you move your lips

But it sounds like gibberish