Genetic analysis of lymphoproliferative disorders

Standardisation of bone marrow staging

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General considerations
Types of genetic analysis at staging

- Cytogenetics
- FISH
- Molecular genetics
  - High-throughput panels
  - MRD
  - Liquid biopsy
- Clinical trials
Different levels of necessity

• Must do if at all possible
  - Result is required for diagnosis
  - Result will impact management (e.g. targeted therapies)

• Could do, under favourable circumstances
  - Result will inform prognosis

• Must NOT do
  - Shotgun genetic testing to look for a diagnosis
  - Have junior doctors “tick all the boxes”
Must do

• All molecular studies at staging must be preceded and guided by a morphological assessment

• Morphology must be done by a haematopathologist where possible

• Genetic analyses must be validated before entering routine practice
Specific LPDs
CLL/SLL in need of treatment

- Applicable tests
  - FISH panel
    - +12; del(17p); del(13q); del(11q)
  - IGHV and TP53 mutation status
  - Karyotyping
- TP53 deletions affect treatment response
  - If ibrutinib, venetoclax, idelalisib, or alemtuzumab are available, TP53 testing should be mandatory
  - Young patients with TP53 lesions are transplant candidates
- Other lesions are prognostic but unlikely to affect treatment

Farooqui et al, Lancet Oncology 2015
FL

- FL is predominantly a morphological diagnosis on lymph node
- W+W pts with normal FBC do not need staging marrow
- Staging marrow indicated in:
  - Patients needing treatment
  - Presence of mild cytopenias without plausible explanation
  - All significant cytopenias regardless of possible other causes
- FISH for t(14;18) and *BCL6* rearrangements occasionally useful
  - If diagnosis is unclear (esp paed cases)
  - Do on LN, not marrow
  - NOT mandatory
- Targeted therapies are NOT influenced by genetic testing
  - Idelalisib, lenalidomide, rituximab, etc.
• Morphological diagnosis on tissue
• ABC vs GCB by IHC
  • ABC vs GCB does not affect first-line management outside clinical trials
  • May affect 2nd line treatment if ibrutinib or bortezomib are available
• Double hit DLBCL
  • Very poor prognosis, needs more than R-CHOP
  • Triple FISH for MYC, BCL2, BCL6 translocations is expensive
  • Restrict to GCB cases that co-express MYC plus BCL2 or BCL6
• BMAT
  • Not needed if marrow is PET negative
  • Recommended in all other scenarios except palliative
    • Can affect prognosis, length of Rx, and CNS prophylaxis

Waldenstrom’s macroglobulinaemia

- BMAT mandatory
- *MYD88* mutations common in WM but not MZL
  - Can be helpful in differentiating
- If ibrutinib is considered:
  - *MYD88*\[^{L265P}/CXCR4^{WT}\] ORR: 100%
  - *MYD88*\[^{L265P}/CXCR4^{WHIM}\] ORR: 85.7%
  - *MYD88*\[^{WT}/CXCR4^{WT}\] ORR: 71.4%
  - Molecular testing should be considered in ibrutinib candidates

Treon et al, NEJM 2015
Hairy cell leukaemia

- BMAT recommended
- *BRAF* mutations seen in almost all non-variant cases
  - Can be detected by IHC or PCR
- Mutation screening is clinically useful IF:
  - The diagnosis is in doubt OR
  - Vemurafenib is considered in relapsed disease

Tiacci et al, NEJM 2015
Lymphoblastic lymphoma (LL)

• Investigations as in ALL
• BMAT mandatory
• FISH for t(9;22) and t(8;14) should be done in all cases
  • This will affect use of TKI in Ph+ LL
  • Although initial chemo for Burkitt and LL is similar in some centres, maintenance therapy is NOT needed for BL
• Karyotyping adds important prognostic information and may guide transplant decision
  • Not a priority in limited resource settings
Other B-cell LPDs

- Mantle cell and Burkitt lymphomas
  - Staging marrow is mandatory
  - FISH for t(11;14) for MCL
  - FISH for t(8;14) and variants in BL
  - Should be performed on diagnostic tissue if at all possible

- Gastric MALT lymphoma
  - FISH for t(11;18)
  - Positive cases are less likely to respond to antibiotics
Hodgkin lymphoma

- No genetic analysis is indicated
- No BMAT required if marrow is negative on PET and no cytopenias are present
- No BMAT required if multifocal PET +ve skeletal areas

- Staging marrow recommended in cytopenic patients with negative PET
- Staging marrow recommended if no access to PET
Anaplastic large-cell lymphoma

• Staging marrow required
• ALK +ve cases have ALK translocations
  • The most common is t(2;5)
• ALK +ve have better prognosis and can be treated with crizotinib
• FISH with BAP for ALK is recommended if possible
  • IHC usually sufficient
  • FISH mandatory if treating with crizotinib
• Invx on diagnostic tissue, not marrow

Passerini et al, JNCI 2014
Clonality studies

• PCR kit
  • Detects rearranged Ig or TCR in the tumour clone
• Used to distinguish malignant vs benign lymphoid aggregates
• Not required in most cases
  • Morphologically obvious malignancy
  • Light chain restriction on flow cytometry
• Useful in T-cell lymphomas
  • Caveat of false positives
• Can distinguish late relapse from second lymphoma
Summary

• Lymphoma diagnosis is usually on LN biopsy
  • BMAT usually for staging

• **Selected** genetic testing can influence management

• Necessity for testing is often dictated by treatment availability

• Balance the value of “prognostic information” vs cost