Lymphoma Network of New Zealand

Splenic Marginal Zone Lymphoma Protocol
(SMZL)

Summary of Recommendation

- **Diagnosis and Staging:**
  - Initial work up includes standard lymphoma investigations.
    - Blood film
    - Bone marrow
    - Tissue (spleen)
  - Staging system

- **Treatment:**
  - Indication for Treatment
  - Potential Therapy:
    - Splenectomy
    - Rituximab Monotherapy
    - R-Bendamustine
    - Rituximab Maintenance
    - Novel Therapy
  - Treatment Considerations

Sub Topics

1. Introduction
   - Epidemiology
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   - Mutational Analyses

2. Diagnosis and Staging
   - Clinical Presentation
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3. Treatment
   - Indication
   - Potential Therapy
   - Treatment Considerations

Introduction

Splenic marginal zone lymphoma is a rare, indolent subtype of lymphoma which accounts for less than 2% of all non-Hodgkin's lymphomas.

Epidemiology:

The median age of presentation is 69 years. There is an association with hepatitis C virus with one Italian paper quoting 18% of patients with SMZL were Hepatitis C positive. Another series of 9 patients with hepatitis C and SMZL was published in NEJM 2002.

- Seven of 9 patients had resolution of SMZL and undetectable HCV RNA with interferon treatment of hepatitis C.

Pathogenesis:

Marginal zone B cells are non-circulating mature B cells that segregate anatomically into the marginal zone (MZ) of the spleen at the interface of the red pulp and white pulp. This region contains multiple subtypes of macrophages, dendritic cells, and the MZ B cells. The MZ B cells within this region typically express high levels of IgM, CD21, CD1, CD9 with low to negligible levels of secreted-IgD, CD23, CD5, and CD11b that help to distinguish them phenotypically from follicular (FO) B cells and B1 B cells. In humans the splenic marginal zone B cells have evidence of somatic hypermutation in their immunoglobulin genes, indicating that they have been generated through a germinal centre reaction to become memory cells.

Similar to B1 B cells, MZ B cells can be rapidly recruited into the early adaptive immune responses in a T cell independent manner.[4] The MZ B cells are especially well positioned as a first line of defence against systemic blood-borne antigens that enter the circulation and become trapped in the spleen.[5] It is believed they are especially reactive to bacterial cell wall components and self-antigens which are the products of aging.[4] MZ B cells also display a lower activation threshold than their Follicluar B cell counterparts with heightened propensity for plasma cell differentiation that contributes further to the accelerated primary antibody response.

Mutational Analyses:

MZ B-cells are the only B-cells dependent on NOTCH2 signalling for proliferation. NOTCH mutations are seen in SMZL at a much higher rate than in other B-cell NHL. All mutations cause impaired degradation of the NOTCH2.

- In a recent study ***MYD88 L265P*** was detected in
    - 13/86 (15%) SMZL
    - 19/24 (79%) LPL
    - Absent from NMZL and MALT cases.
- SMZL cases positive for MYD88 L265P are also associated with monoclonal IgM paraproteinemia (4/13 cases; $P<0.0283$).
    - The boundary between MYD88 positive SMZL and MYD88 positive Lymphoplasmacytic lymphoma (LPL) is grey and may change.
    - MYD88 positivity is rarely if at all seen in other marginal zone lymphomas.

Diagnosis and Staging

Clinical Presentation:

Splenomegaly is the presenting feature in almost all patients; anaemia-related symptoms and B symptoms are rare.

The disease commonly pursues an indolent course with the median overall survival exceeding 10 years, but the disease can follow a more aggressive course in a significant subset of patients.

Establishing Diagnosis:

- **Blood smear:**
  - The presence of circulating villous lymphocytes defines splenic lymphoma with villous lymphocytes.
  - Patients with a CD5+ marginal zone lymphoma have a tendency to higher lymphocyte counts but no difference in outcome.

- **Bone marrow:**
  - The bone marrow shows an intrasinusoidal pattern of infiltration on bone marrow biopsy.

- **Splenectomy:**
  - Can be useful as both a diagnostic tool and definite treatment for patient
  - The spleen shows a B cell lymphoma infiltrate in the marginal zone between the white pulp and the red pulp.

Staging:

Initial staging investigations should include routine blood test as per lymphoma guidelines, staging CT and a bone marrow biopsy.

Treatment

Indication for Treatment:

- Progressive or painful splenomegaly
- Progressive or severe cytopenias
    - Hb <100g/L
    - Neutrophils <1.0 x10E9/L
    - Platelets <100 x10E9/L
- Constitutional symptoms

Potential Therapy:

1. **Splenectomy**

   Long term follow-up of 100 patients, 98 of whom had both spleen and marrow involvement was treated with splenectomy alone[1].
   - The progression free survival (PFS) was 61% and 47% at five and ten years respectively.

   The addition of R-CHOP did not improve CR or PFS rate. The excellent outcomes with rituximab monotherapy (see below) have meant the splenectomy as front-line therapy is less favoured than in the past.

2. **Rituximab monotherapy (funded for 6 doses)**

   375 mg/m2 x 6 cycles +/- by one to two years (two monthly) maintenance Rituximab[2].
   - End of Induction
       - ORR 92% (98/106), CR 44% (47/106), CRu 21% (22/106) and PR 27% (29/106)
       - Median time to resolution of splenomegaly and haematological response is 4 and 2 weeks respectively.
   - End of Maintenance (1 or 2 years)
       - CR 70% (54/77), CRu 18% (14/77)and PR 10% (8/77)
           - Maintenance therapy improve the depth of response in 21% (16/77)
       - There was equivalent progression free survival advantage with one year maintenance versus two years.
   - Long Term Outcome
       - 5 and 10 year FFP rates were 71% and 64% respectively
           - 5 and 9 year FFP rates in maintenance group were 79% and 76% respectively
           - 5 and 9 year FFP rates in non-maintenance group were 52% and 42% respectively (possible selection bias – maintenance given for responders only)

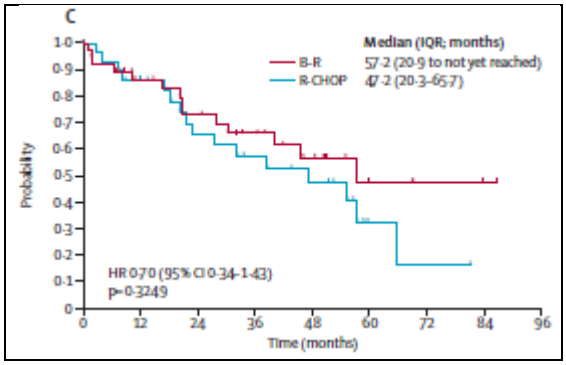
- 5 and 10 year OS rates were 93% and 85% respectively.

- Refer to Treatment Consideration (below) regarding current funding restrictions.

3. R- Bendamustine

The data supporting BR in SMZL is limited due to the limitation of the studies supporting BR over R-CHOP/R-CVP. The two frequently quoted studies are StiL[3,4] and Bright[5,6] study. The main limitation is that marginal zone lymphoma (let along SMZL) only makes up a small proportion of the comparison arm and results are from sub-group analysis.

- In StiL Study (MZL subgroup)[3]
  - BR (n=37) vs R-CHOP (n=30)
  - No significant PFS difference between two groups.
  - Benefit due to less toxicity.



- In Bright Study (MZL subgroup)[5]

	BR	R-CHOP/R-CVP
N	28	18
CR	20%	24%
ORR (CR+PR)	92%	71%
PFS		

  - No statistical analysis provided from the original paper (presume not powered for subgroup analysis).
  - In the recent update there is some concern with increased malignancy in the BR group[6]. This was not reported in the updated STiL study[4].

Bright study showed a superior outcome for R-Bendamustine over R- CHOP or R-CVP in the marginal zone lymphoma subset.

- The 3 year PFS and OS were 90 and 98% respectively.

The BRISMA/IELSG 36 study[7] is an open label, single arm phase II study specifically looking at response rate in SMZL patient treated with BR in a frontline setting.

- N = 56
- ORR 91% and CR 73%
- 3 year DOR (93%), PFS (90%) and OS (96%)

4. Maintenance Rituximab (currently not funded in NZ)

Rituximab maintenance has been shown to improve the depth of response and prolonged PFS after rituximab monotherapy (see above). The benefit of maintenance rituximab after BR was shown in the MAINTAIN trial[8] (this include all MZL and not just SMZL).

- StiL NHL7-2008 MAINTAIN trial[8]
    - BR Induction
        - ORR 91% and CR 19%
    - R Maintenance (2 monthly for 2 years)
        - Median PFS not reached in maintenance group vs 92.2m in observation and is statistically significant (HR 0.35).
        - OS rate at 6 years was 92% vs 86% in favour of maintenance group but this is not statistical significant.

5. Novel Therapy (currently not funded)

Bruton tyrosine kinase (BTK) inhibitor

- Ibrutinib 560 mg daily has activity in relapsed marginal zone lymphomas, including SMZL[9].
    - ORR 48% and PFS 14.2 months.
    - FDA approved for patients with SMZL who have progressed after one prior line of chemotherapy.
- Zanubrutinb 160mg BD has also shown activity in MZL.

BH2 Inhibitor (Venetoclax)

- Data on venetoclax in SMZL is limited but it does seem to have activity when given alone or with R-bendamustine[10,11].
- Combination of venetoclax with a BTK inhibitor has not been trialled to date in MZL.

Treatment Considerations:

Rituximab x 6 cycles offers a quick response with high (~90%) overall response rates and CR rates (~40%) it is an appealing alternative to splenectomy in frontline therapy and is the favoured approach.

Maintenance Rituximab is not currently funded in NZ although effective at prolonging the duration of response. Rituximab maintenance for 1 or 2 years is recommended after Rituximab or R-bendamustine induction.

R-Bendamustine has similar response rate to Rituximab alone but responses are deeper and more durable. The difference in outcomes is less if Rituximab maintenance is give following Rituximab induction. Salvage treatment at relapse with R-bendamustine or the newer agents below makes duration of response less critical. R-bendamustine could be considered if depth or response matters and Rituximab maintenance is not available.

Transformed Disease:

High grade transformation should be managed with R-CHOP.

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