Mantle Cell Lymphoma (MCL)

PATHOLOGIC DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one tumor paraffin block. Hematopathology confirmation of classic versus aggressive variant of MCL (blastoid/pleomorphic). Re-biopsy if consult material is non-diagnostic.
- Adequate immunophenotype to confirm diagnosis[1]
  - Paraffin panel[2] **or** flow cytometry immunophenotyping: kappa/lambda light chains, CD5, CD10, CD19, CD20, CD23, FMC-7, CD200, and CD43
    and
  - Ki-67 (proliferation rate)

OF USE IN CERTAIN CIRCUMSTANCES:

- Molecular genetic analysis
  - Somatic hyper-mutation for IGHV gene rearrangement and mutation status
  - *TP53*
  - *NOTCH1*
  - *NOTCH2*
  - *NSD2*
  - *BTK*
  - *KMT2D*
- Immunohistochemistry for *SOX-11* and *CD23*
- FISH to detect t(11;14)(q13;q32)/*CCND1::IGH, TP53*, and *MYC*

STRONGLY RECOMMENDED:

- Fine needle aspiration (FNA) or core biopsy for tissue banking by protocol

FISH = fluorescence in situ hybridization

[1] Immunophenotype: CD5+, CD20+, CD43+, CD200-/+, ROR1+/-, CD23-/+, cyclin D1+.
Note: Some cases of Mantle Cell Lymphoma may be CD5-, CD10+, or CD23+.
If the diagnosis is suspected, cyclin D1 staining or FISH to demonstrate t(11;14)(q13;q32) should be performed.

[2] Upon tissue availability, consider Pan B-cell marker (CD19, CD20, PAX5), CD3, CD5, CD10, and cyclin D1.

[3] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

[4] Obtain 4-6 biopsies from each of the following areas during EGD/colonoscopy: duodenum including duodenal bulb, gastric antrum, gastric body, terminal ileum, throughout the colon including right, left and transverse, rectum

INITIAL EVALUATION

ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, size of liver and spleen, and patient's age
- Performance status (ECOG)
- B symptoms (fever, drenching night sweats, unintentional weight loss)
- CBC with differential, LDH, BUN, creatinine, albumin, AST, ALT, alkaline phosphatase, total bilirubin, indirect bilirubin, serum magnesium, serum calcium, uric acid, aPTT, prothrombin time and INR
- Urianalysis
- IgM, IgG, IgA
- Screening for HIV 1 and 2, hepatitis B and C (HBcAb, HBsAg, HCVAb)
- Beta-2 microglobulin (B2M)
- Chest x-ray, PA and lateral
- Bone marrow unilateral biopsy with unilateral aspirate
- PET/CT with contrast (preferred)
  - CT neck, chest, abdomen and pelvis with contrast (if PET-CT is not feasible)
- Lifestyle risk assessment[3]

OF USE IN SELECTED CASES:

- Protein electrophoresis
- EGD/colonoscopy with segmental biopsies[4]
- Plain bone radiographs and bone scan
- CT head with contrast or MRI brain
- Discuss fertility preservation options and sperm banking for patients of child bearing potential
- Lumbar puncture
- Colonoscopy
- Urine pregnancy test
- Referral(s) as indicated:
  - Cardiology to screen for cardiac related comorbidities specially for atrial fibrillation, hypertension, and major EKG abnormalities
  - Genetics to screen for family history of hematologic or other cancers
  - Dermatology to screen for secondary skin cancers

Induction Therapy for untreated MCL see Page 2

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Mantle Cell Lymphoma (MCL)

Note: Consider Clinical Trials as treatment options for eligible patients.

PRESENTATION

Untreated MCL

MD Anderson high risk factors[1] present?

Yes

Age less than or equal to 65?

Yes

- Clinical trial
- Window-1 regimen[2] and/or Window-2 regimen (off-protocol)
- R-HCVAD/R-MA[2]
- Radiation therapy[3] (if early Stage I or II)
- R-bendamustine with radiation therapy (if early Stage I or II)
- R-CHOP/R-DHAP[2] followed by autologous stem cell transplant
- Lenalidomide with rituximab
- R-BAC[2]

No

- Clinical trial
- R-bendamustine with or without maintenance rituximab every 2 months **and/or** radiation therapy if early Stage I or II
- Ibrutinib with rituximab (cardiology consultation to clear patient)
- Lenalidomide with rituximab
- R-BAC[1]
- VR-CAP[2]
- R-CHOP[2]

No

See Page 3 for patients with no or low risk factors

FOLLOW-UP

Follow-up:

- Year 1: Every 3 months
  - CBC with differential, complete metabolic panel (CMP), LDH, Beta-2 microglobulin (B2M), and other labs as clinically indicated
  - CT chest, abdomen, and pelvis with contrast or PET/CT with contrast (if feasible) until negative or clinically indicated
  - Unilateral bone marrow biopsy and aspiration until negative or clinically indicated
- Years 2 and 3: Every 4 months
  - CBC with differential, CMP, LDH, B2M, and other clinically warranted labs
  - CT chest, abdomen, and pelvis with contrast or PET/CT with contrast (if feasible) until negative or clinically indicated
- Years 4 and 5: Every 6 months
  - CBC with differential, CMP, LDH, B2M, and other clinically warranted labs
  - CT chest, abdomen, and pelvis with contrast or PET/CT with contrast (if feasible) until negative or clinically indicated
- After years 5: Annually
  - CBC with differential, CMP, LDH, B2M, and other labs as clinically indicated
  - CT chest, abdomen, and pelvis with contrast or PET/CT with contrast (if feasible) until negative or clinically indicated
- GI colonoscopy and upper GI endoscopy with random biopsies (if initially involved or if clinically indicated), repeat after 12 months if initial positive with random biopsies

Relapsed or refractory MCL, see Page 4

[1] High Risk factors: Blastoid/pleomorphic histology, *TP53* mutation or *del17p* by FISH, complex karyotype, MYC positive by FISH, bulky tumor > 7 cm and spleen > 20 cm, Ki-67 ≥ 30% in tissue biopsy

[2] Chemotherapy regimen abbreviations, see Appendix A

[3] The recommended radiation dose is 24 Gy

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Mantle Cell Lymphoma (MCL)

Note: Consider Clinical Trials as treatment options for eligible patients.

PRESENTATION

Patient with no or low risk factors

Age less than or equal to 65?

INITIAL THERAPY

Yes

- Observation[1] or clinical trial for low risk smoldering MCL
- Window-1 regimen[2] (off-protocol)
- Window-2 regimen[2] (off-protocol)
- R-bendamustine with radiation therapy (if early Stage I or II)
- R-CHOP/R-DHAP[2] **or** R-HCVAD/R-MA[2] followed by autologous stem cell transplant
- Lenalidomide with rituximab
- Ibrutinib with rituximab

No

- Observation[1] or clinical trial for low risk smoldering MCL
- R-bendamustine with or without maintenance rituximab every 2 months **and/or** radiation therapy if early Stage I or II
- Ibrutinib with rituximab
- Lenalidomide with rituximab
- R-BAC[2]

FOLLOW-UP

Follow-up:

- Year 1: Every 3 to 4 months
  - CBC with differential, complete metabolic panel (CMP), LDH, Beta-2 microglobulin (B2M), and other labs as clinically indicated
  - CT chest, abdomen, and pelvis with contrast or PET/CT with contrast (if feasible) until negative or clinically indicated
  - Unilateral bone marrow biopsy and aspiration until negative or clinically indicated
- Years 2: Every 4 to 6 months
  - CBC with differential, CMP, LDH, B2M, and other clinically warranted labs
  - CT chest, abdomen, and pelvis with contrast or PET/CT with contrast (if feasible) until negative or clinically indicated
- Years 3, 4 and 5: Every 6 months
  - CBC with differential, CMP, LDH, B2M, and other clinically warranted labs
  - CT chest, abdomen, and pelvis with contrast or PET/CT with contrast (if feasible) until negative or clinically indicated
- After years 5: Annually
  - CBC with differential, CMP, LDH, B2M, and other labs as clinically indicated
  - CT chest, abdomen, and pelvis with contrast or PET/CT with contrast (if feasible) until negative or clinically indicated
- GI colonoscopy and upper GI endoscopy with random biopsies (if initially involved or if clinically indicated), every 6 months until negative results[1]

Relapsed or refractory MCL, see Page 4

[1] Initial GI scopes with biopsies may be needed to help decide on observation or therapy
[2] Chemotherapy regimen abbreviations, see Appendix A

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Mantle Cell Lymphoma (MCL)

Note: Consider Clinical Trials as treatment options for eligible patients.

TREATMENT

A

Relapsed or refractory MCL

- Clinical trial
- BTK inhibitors
  - Ibrutinib with or without rituximab
  - Acalabrutinib
  - Zanubrutinib
- Anti-CD19 CAR-T Cell Therapy
  - Brexucabtagene autoleucel
- Venetoclax with or without rituximab
- Venetoclax with ibrutinib
- Ibrutinib, lenalidomide, rituximab
- Salvage chemotherapy
  - R-BAC[1]
  - VR-CAP[1]
  - R-CHOP[1]
  - R-HCVAD[1] with or without R-MA
  - R-DHAP[1]
  - Rituximab, gemcitabine and oxaliplatin
  - Lenalidomide with rituximab
  - Bendamustine with rituximab
  - R-ICE[1]
- Consider radiation therapy alone or chemoradiation to bulky tumors[2]

→ Response?

Yes →
- Clinical trial
- Allogeneic stem cell transplant, if eligible and if high risk features

→ Relapse?

Yes →
- Clinical trial
- Alternative regimen not previously given (see Box A)
- Supportive care
- Therapy plus donor lymphocyte infusion (DLI) if prior allogeneic transplant

No → Monitor per stem cell transplant

No →
Perform genomic/ transcriptomic testing from biopsy at relapse for possible targets

→ Possible Targets?

Yes → Clinical trial

No →
- Allogeneic stem cell transplant, if eligible
- Alternative regimen not previously given (see Box A)

[1] Chemotherapy regimen abbreviations, see Appendix A

[2] The preferred initial radiation dose is 4 Gy. Consider higher dose of 20-24 Gy for non-responders to 4 Gy.

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APPENDIX A: Chemotherapy Regimen Abbreviations

Window-1: ibrutinib and rituximab followed by 4 cycles of R-HCVAD/R-MA
Window-2: ibrutinib-rituximab and venetoclax (IRV) followed by risk stratified R-HCVAD
- Low Risk: only IRV maintenance for up to 2 years
- Intermediate Risk: 2 cycles of R-HCVAD/R-MA followed by IRV maintenance up to 2 years
- High Risk: 4 cycles of R-HCVAD/R-MA followed by IRV maintenance up to 2 years

R-HCVAD: rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone, and (mesna); alternating with R-MA
R-MA: rituximab, methotrexate, and cytarabine; alternating with R-HCVAD
R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-DHAP: rituximab, dexamethasone, cytarabine, and cisplatin
R-BAC: rituximab, bendamustine, and low-dose cytarabine
R-ICE: rituximab, ifosfamide, carboplatin, and etoposide
VR-CAP: bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone

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