Discussion

Chronic Lymphocytic Leukemia/
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Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A)

Supportive Care for NHL (NHODG-B)

Lugano Response Criteria for Non-Hodgkin’s Lymphoma (NHODG-C)

Principles of Radiation Therapy (NHODG-D)

Special Considerations for the Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib) (NHODG-E)

Primary CNS Lymphoma (See NCCN Guidelines for CNS)
Waldenström’s Macroglobulinemia/Lymphoplasmacytic Lymphoma (See NCCN Guidelines for WM/LPL)
Updates in Version 2.2015 of the NCCN Guidelines for Non-Hodgkin's Lymphomas from Version 1.2015 include:

**New Guideline**

**CD-1**
- A new guideline for the treatment of Castleman's Disease was added.

**Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**

**CSLL-D 1 of 7**
- Footnote g was added, “Data from the CLL10 study confirms the superiority of FCR over BR in younger patients. For patients >65 y, the outcome was similar for both regimens with less toxicity for BR. BR may be a reasonable alternative for older patients otherwise eligible for chemoimmunotherapy and is associated with fewer myelosuppressive toxicities.” Also for CSLL-D 4 of 7.

**CSLL-E**
- Response Definition after Treatment for CLL
  - Footnote c was added. “MRD-negative status in peripheral blood (PB) correlates with better PFS. Analysis from GCLLSG study indicates that if PB is MRD negative, residual splenomegaly has no clinical significance. Kovacs G, Boettcher S, Bahlo J, et al. Blood 2014;124:Abstract 23.”

**Mantle Cell Lymphoma**

**MANT-3**
- Not candidate for HDT/ASCR
  - For both treated with RCHOP and Not treated with RCHOP, “or BR” was added.
  - For rituximab maintenance, the category 1 was clarified as “following RCHOP.”

**MANT-A 1 of 3**
- Induction therapy, Less aggressive therapy
  - Bendamustine + rituximab was revised by adding “± maintenance rituximab.”

**Diffuse Large B-cell Lymphomas**

**BCEL-3**
- Footnote k was revised, “In selected cases (paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, kidney or adrenal gland involvement, concurrent expression of MYC and BCL2 protein... See Prognostic Model for Assessing Risk of CNS Disease (BCEL-A 2 of 2).”

**BCEL-A 2 of 2**
- A new table was added, “Prognostic Model to Assess the Risk of CNS Disease.”

**MS-1**
- The CLL/SLL discussion section has been updated to reflect the changes in the algorithm.
Updates in Version 1.2015 of the NCCN Guidelines for Non-Hodgkin’s Lymphomas from Version 5.2014 include:

Global changes
- Suggested treatment regimen references were updated throughout the guidelines.
- Work-up, Essential, bullets for “Chest/abdominal/pelvic CT with contrast of diagnostic quality and PET-CT scan” were combined as “Chest/abdominal/pelvic CT with contrast of diagnostic quality and/or PET-CT scan” on FOLL-2, BCEL-2, AIDS-2, and NKTL-1.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

CSLL-1
- Informative for prognostic and/or therapy determination
  - Stimulated cytogenetics, “complex karyotype” was added.
  - Determination of CD38 and ZAP-70, “methylation” was added as an option.
  - Footnote “f” was revised by adding, “Methylation status is not widely available outside of a clinical trial”

CSLL-3
- For CLL Rai High (III-IV) Risk, “Progressive Cytopenias” was added.
- Footnotes
  - Footnote “j” was added, “Increased prolymphocytes in blood (>5%-<55%) (so-called “CLL-PL” or CLL with increased prolymphocytes) as well as the presence of expanded proliferation centers (broader than a 20x field) or a high proliferation rate (either >2.4 mitoses/proliferation center or Ki-67 >40%/proliferation center) on lymph node biopsy (so-called “accelerated CLL”) are associated with more aggressive disease and poorer outcome; neither of these findings is considered to represent Richter’s transformation and optimal management has not been established.”
  - Footnote “n” was added, “Select patients with mild, stable cytopenia (ANC<1000/μL, Hgb <11 g/dL, or PLT <100,000/μL) may continue to be followed with observation.”

CSLL-4
- Footnote was removed, “If long response, treat with the same first-line therapy. If short response, consider alternative first-line therapy not used before.”

CSLL-5
- The qualifiers for age and comorbidities for CLL without del (11q) or del (17p) and CLL with del (11q) were clarified as follows:
  - Age ≥70 years and younger patients with significant comorbidities
  - Age <70 years and older without significant comorbidities
- After first-line therapy, “Relapsed CLL with indication for treatment (See CSLL-3)” was added.
- The response to therapy that included a separation of short and long response was removed along with corresponding footnotes.

CSLL-6
- First-line therapy
  - The first sub-bullet was revised, “17p deletion is associated with low response rates with chemoimmunotherapy all treatments...”
  - Response to therapy
    - “CR/PR” was replaced with “Response.”
    - Response, “allogeneic stem cell transplant” was modified by adding “consider.”
  - Relapsed/refractory therapy
    - CR and PR options were combined and replaced with “Response” and “See Suggested Regimens” was removed as an option for therapy.
    - An option for “no transplant (progression)” was added.

CSLL-7
- First-line therapy
  - The first bullet was revised by adding, “Outcomes are more favorable in patients who receive chemoimmunotherapy regimens containing an alkylator alkylating agent.”
  - Relapsed/refractory therapy
    - CR and PR options were combined and replaced with “Response” and “See Suggested Regimens” was removed as an option for therapy.

CSLL-A
- Table regarding complex karyotype was added with a corresponding footnote “d”.

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Updates in Version 1.2015 of the NCCN Guidelines for Non-Hodgkin’s Lymphomas from Version 5.2014 include:

**CSLL-D 1 of 7**
- Frail patient, significant comorbidity:
  - “Obinutuzumab + chlorambucil” was changed from a category 2A to a category 1 recommendation.
  - “Ofatumumab + chlorambucil” was added as a category 2A recommendation.
  - “Obinutuzumab” was added as a category 2B recommendation.
  - “Pulse corticosteroids” was changed from a category 2A to a category 3 recommendation.
- CLL without del (11q) or del (17p):
  - First-line therapy, Age ≥70 y and younger patients with significant comorbidities
    - “Obinutuzumab + chlorambucil” was changed from a category 2A to a category 1 recommendation.
    - “Ofatumumab + chlorambucil” was added as a category 2A recommendation.
    - “Obinutuzumab” was added as a category 2B recommendation.
    - “Chlorambucil” was changed from a category 2A to a category 2B recommendation.
    - “Rituximab” was changed from a category 2A to a category 2B recommendation.
    - “Cladribine” was changed from a category 2A to category 3 recommendation.
  - Age <70 y without significant comorbidities
    - “FCR” was changed from a category 2A to a category 1 recommendation.
    - “Obinutuzumab + chlorambucil” was removed.

**Footnotes:**
- Footnote “j” was added: “In rare circumstances of CNS disease, cladribine is potentially useful.”

**CSLL-D 2 of 7**
- CLL without del (11q) or del (17p):
  - Relapsed/refractory therapy, the use of short and long response was removed.
  - Relapsed/refractory therapy, Age ≥70 y and younger patients with significant comorbidities
    - “Ibrutinib” was changed from a category 2A to a category 1 recommendation.
    - Idelalisib + rituximab was changed to “idelalisib ± rituximab”
    - “Obinutuzumab” was added as a category 2A recommendation.
  - Relapsed/refractory therapy, Age <70 y without significant comorbidities
    - “Ibrutinib” was changed from a category 2A to a category 1 recommendation.
    - Idelalisib + rituximab was changed to “idelalisib ± rituximab”
    - “Obinutuzumab” was added as a category 2A recommendation.
- Footnote
  - Footnote “j” was revised by adding, “While alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use.”

**CSLL-D 3 of 7**
- CLL with del (17p):
  - First-line and relapsed/refractory therapy were put in order of preference.
  - Relapsed/refractory therapy
    - “Idelalisib + rituximab” was changed to “idelalisib ± rituximab”
    - “RCHOP” was removed
    - “CFAR” was removed.
- CLL with del (11q):
  - First-line therapy, Age ≥70 y and younger patients with significant comorbidities
    - “Obinutuzumab + chlorambucil” was changed from a category 2A to a category 1 recommendation.
    - “Ofatumumab + chlorambucil” was removed.
    - “Cyclophosphamide, prednisone ± rituximab” was removed.
    - “Fludarabine ± rituximab” was added as a category 2A recommendation.
    - “Chlorambucil” was added as a category 2B recommendation.
    - “Rituximab” was changed from a category 2A to category 3 recommendation.
    - “Cladribine” was changed from a category 2A to category 3 recommendation.
  - Age <70 y without significant comorbidities
    - “FCR” was changed from a category 2A to a category 1 recommendation.
    - “Obinutuzumab + chlorambucil” was removed.

**Footnotes:**
- Footnote “j” was added: “In rare circumstances of CNS disease, cladribine is potentially useful.”

**CSLL-D 4 of 7**
- CLL with del (17p):
  - First-line therapy, Age ≥70 y and younger patients with significant comorbidities
    - “Obinutuzumab + chlorambucil” was changed from a category 2A to a category 1 recommendation.
    - “Ofatumumab + chlorambucil” was added as a category 2A recommendation.
    - “Rituximab” was changed from a category 2A to category 3 recommendation.
Updates in Version 1.2015 of the NCCN Guidelines for Non-Hodgkin’s Lymphomas from Version 5.2014 include:

**CSLL-D 5 of 7**
- CLL with del (11q):
  - Relapsed/refractory therapy, the use of short and long response was removed.
  - Relapsed/refractory therapy, Age ≥70 and younger patients with significant comorbidities
    - “Ibrutinib” was changed from a category 2A to a category 1 recommendation.
    - “Idelalisib + rituximab” was changed to “idelalisib ± rituximab”
    - “Obinutuzumab” was added as a category 2A recommendation.
  - Relapsed/refractory therapy, Age <70 y without significant comorbidities
    - “Ibrutinib” was changed from a category 2A to a category 1 recommendation.
    - “Idelalisib + rituximab” was changed to “idelalisib ± rituximab”
    - “RCHOP” was removed.
    - “Obinutuzumab” was added as a category 2A recommendation.

**CSLL-E**
- Definition for partial response was changed from “at least two of the criteria of group A plus one of the criteria of group B have to be met” to “Requires 1) having two of the group A criteria if 2 or more are present. Patients with one group A criteria (excluding bone marrow) are also considered evaluable for response; 2) one group B criteria whether or not normal from baseline prior to starting therapy.”

**FOLLL-1**
- Diagnosis, Useful Under Certain Circumstances
  - 3rd bullet regarding IHC: “IRF4/MUM1 for FL grade 3” was added.
  - Footnote “a” was revised by adding, “However, controversy exists regarding management of FL grade 3. Some may treat FL grade 3a as follicular lymphoma and others may treat it as DLBCL.” (Also added as footnote “g” to BCEL-1)

**FOLL-2**
- Workup
  - “PET-CT scan” was moved from Useful in Selected Cases to Essential with “Chest/abdominal/pelvic CT with contrast of diagnostic quality.”

**FOLL-4**
- Stage II bulky, III, IV:
  - After observe, surveillance imaging was clarified as, “Up to 2 y post completion of treatment: CT scan no more than every 6 mo.”

**FOLL-5**
- First heading was changed from “Initial Response” to “End-of-treatment Response.”

**FOLL-6**
- Histologic transformation to diffuse large B-cell lymphoma
  - For minimal or no prior chemotherapy,
    - For no response to progressive disease, after radioimmunotherapy,
      - “or see BCEL-C (Second-line therapy)” was added.

**FOLL-B 1 of 3**
- All of the regimens for FL are now listed in order of preference.
  - First-line therapy
    - “Lenalidomide + rituximab” was added as a category 3 recommendation.
    - First-line Therapy for Elderly or Infirm
      - Radioimmunotherapy was changed from a category 2A to a category 2B recommendation.
      - First-line Consolidation or Extended Dosing (optional)
        - “Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)” was changed from a category 1 to a category 2A recommendation.
  - Second-line and Subsequent Therapy
    - “FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) (category 1)” was removed.

**Gastric MALT Lymphoma**

**MALT-1**
- Workup, “Hepatitis C testing” was moved from Useful in Selected Cases to Essential.

**MALT-2**
- Stage I_E1 was combined with Stage I_E2 or Stage II_E H. Pylori positive.

**Nongastric MALT Lymphoma**

**NGMLT-1**
- Workup, “Hepatitis C testing” was moved from Useful in Selected Cases to Essential.

**Nodal Marginal Zone Lymphoma**

**NODE-1**
- Workup, “Hepatitis C testing” was moved from Useful in Selected Cases to Essential.
**Updates in Version 1.2015 of the NCCN Guidelines for Non-Hodgkin’s Lymphomas from Version 5.2014 include:**

**Mantle Cell Lymphoma**

**MANT-1**
- Diagnosis, Useful Under Certain Circumstances
  - “IHC for SOX11” was added.

**MANT-3**
- Stage II bulky, III, IV, partial and complete response were combined and footnote “l” was added, “Consider second-line therapy to improve partial response.”

**Diffuse Large B-Cell Lymphoma**

**BCEL-2**
- Workup:
  - “Beta-2-microglobulin” was moved from Essential to Useful in Selected Cases.
  - Bullet revised, “Adequate bone marrow biopsy (>1.6 cm) ± aspirate; bone marrow may not be needed if PET scan negative unless finding of another lymphoma subtype is important for treatment decision.”
  - Useful in Selected Cases, “Lumbar puncture” was clarified by adding, “consider if paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, or ≥2 extranodal sites and elevated LDH.”

**BCEL-3**
- Stage I, II
  - The cutoff for Nonbulky and Bulky disease was revised, “Nonbulky (<7.5 cm <40-em) and “Bulky (≥7.5 cm ≥40 em).”

**BCEL-4**
- Partial response, Follow-up therapy, “If PET+ after 6 cycles of RCHOP” was added to “high-dose therapy with autologous stem cell rescue ± RT pre- or post- transplant.”
- Footnotes
  - Footnote “s” was added: “PET-CT scan should be interpreted via the PET Five Point Scale (See NHODG-C 3 of 3)” (Also for BCEL-5)
  - Footnote u was removed, “There is evidence that addition of maintenance rituximab does not improve survival.”

**BCEL-5**
- Stage III, IV
  - After end-of-treatment restaging with a complete response, “Preferred” was removed from “Observation.”

**BCEL-6**
- Non-candidates for high-dose therapy, “best supportive care” was added as an additional therapy option.
  - Relapse #2 or greater
    - The option of “alternative second-line therapy (See BCEL-C) or Palliative RT or Best supportive care” was added.
    - All of the options in relapse #2 or greater are choices for patients with intention to proceed to high-dose therapy with either no response after second-line therapy or treatment with consolidation with high-dose therapy with autologous stem cell rescue after a complete/partial response to second-line therapy. Also for non-candidates for high-dose therapy, after second-line therapy, the options for relapse #2 or greater are now available.

**BCEL-A**
- The National Comprehensive Cancer Network-International Prognostic Index (NCCN-IPI)” was added.

**BCEL-B 2 of 2**
- Grey Zone Lymphoma
  - Prognosis and Treatment, 4th bullet was revised, “Data from the NIH suggest that the use of rituximab-anthracycline-based chemotherapy as in other B-cell lymphomas (See BCEL-C) dose-adjusted R-EPOCH is helpful. If localized disease, then ± RT.”

**BCEL-C 1 of 4**
- First-line consolidation, “Double-hit DLBCL: High-dose therapy with autologous stem cell rescue” was added.

**BCEL-C 2 of 4**
- The headings for “Second-line therapy” were clarified as, “Second-line and Subsequent Therapy.”
  - Second-line and Subsequent Therapy (non-candidates for high-dose therapy)
    - “Brentuximab vedotin for CD30+ disease” was added as a category 2B recommendation.

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NCCN Guidelines Version 2.2015 Updates
Non-Hodgkin’s Lymphomas

Updates in Version 1.2015 of the NCCN Guidelines for Non-Hodgkin's Lymphomas from Version 5.2014 include:

**Burkitt Lymphoma**

**BURK-A 1 of 2**

- Second-line therapy:
  - “Rituximab” was added to “High-dose cytarabine.”

**AIDS-Related B-cell Lymphomas**

**AIDS-1**

- Diagnosis, Useful Under Certain Circumstances
  - “KSHV LANA-1” was added.

**AIDS-2**

- Workup, Essential
  - “Hepatitis C testing” was added with a corresponding footnote, “Hepatitis C antibody and if positive, viral load and consult with hepatologist.”
  - Lumbar puncture was clarified by adding, “except for primary effusion lymphoma (PEL) and early stage DLBCL.”
  - Workup, Useful in Selected Cases
    - “Quantitative immunoglobulins” was added.

**AIDS-3**

- The text in the box was revised, “Antiretrovirals can be administered safely with chemotherapy, however, some regimens have recommended discontinuation but consider changing HAART to non-protease inhibitor-based or CYP3A4-neutral regimen to minimize interactions with chemotherapy. Any change in antiretroviral therapy should be done in consultation with HIV specialist. Concurrent HAART associated with higher CR rates (Barta et al. Blood 2013, 122:3251-3262).” (Also for AIDS-4)
- The bullet regarding CD4 count was revised, “If CD4 <100, consider eliminating rituximab; benefit of rituximab less clear due to increased infectious complications.”
- Footnote d was removed, “In patients on active antiretrovirals treated with rituximab-based regimens, low CD4 count (<100/mcL) may be associated with decreased response and survival outcomes; CD4 count <50/mcL has been associated with increased treatment-related deaths.

**AIDS-4**

- Primary CNS lymphoma
  - 1st bullet was added, “Initiate HAART, if not already receiving”
  - 2nd bullet was revised by adding, “Even with poorly controlled HIV and/or marginal performance status, consider high-dose methotrexate.”
  - 4th bullet was revised, “Consider RT alone for palliation of patients who are not candidates for systemic therapy.”

**AIDS-A**

- Supportive Care for AIDS-related B-cell lymphomas is new to the Guidelines.

**Primary Cutaneous B-Cell Lymphomas**

**CUTB-1**

- Workup
  - “PET-CT scan” was moved from Useful in Selected Cases to Essential with “CE Chest/abdominal/pelvic CT and/or PET-CT scan.”

**CUTB-2**

- The response to therapy section was extensively revised due to the combining with the relapse disease algorithm.
- Initial therapy
  - Solitary/regional, the first treatment option was revised, “Local RT (preferred) and/or Excision.”
  - Generalized disease, “Palliative chemotherapy such as chlorambucil ± rituximab or CVP ± rituximab” was revised to “Other systemic therapy.”
- Footnotes
  - Footnote “i” was added, “Local RT is not preferred for relapsed disease.”
  - Footnote “i” was added, “Considered appropriate in asymptomatic patients.”

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Updates in Version 1.2015 of the NCCN Guidelines for Non-Hodgkin’s Lymphomas from Version 5.2014 include:

Peripheral T-Cell Lymphomas

TCEL-3
- Induction Therapy:
  - Radiation therapy was clarified as “ISRT” on this page.

TCEL-4
- Relapse #2 or greater
  - The option of “alternative second-line therapy (See TCEL-B)” was added.
  - All of the options in relapse #2 or greater are choices for patients with intention to proceed to high-dose therapy with either no response after second-line therapy or treatment with consolidation with transplant after a complete/partial response to second-line therapy. Also for non-candidates for high-dose therapy, after second-line therapy, the options for relapse #2 or greater are now available.

TCEL-B 1 of 3
- First-line therapy:
  - For other histologies
    - The regimens were put into “preferred regimen (in alphabetical order)” and “alternative regimens (in alphabetical order)” categories.
    - “CHOP followed by ICE (ifosfamide, carboplatin, etoposide)” was removed.
  - First-line consolidation
    - Statement was revised, “Patients with low IPI ALCL, ALK + disease in remission do not need consolidative transplant, is a subtype with good prognosis does not need consolidative transplant if in remission.”
    - Footnote “c” was added, “CHOP followed by IVE regimen includes HSCT.”

TCEL-B 2 of 3
- Second-line therapy:
  - The headings for “Second-line therapy” was clarified by adding, “Second-line and Subsequent Therapy.”
  - For both intention to proceed to high-dose therapy and non-candidate for high-dose therapy, “Bendamustine” was added.
  - Intention to proceed to high-dose therapy
    - “Brentuximab vedotin for systemic CD30+ PTCL” was changed from a category 2B to a category 2A recommendation.
    - “MINE” regimen was removed.
  - Non-candidate for high-dose therapy
    - “Bortezomib” was changed from a category 2A to a category 2B recommendation.

Mycosis Fungoides/Sezary Syndrome

MFSS-1
- Workup:
  - Essential, Imaging studies
    - The qualification for when to perform “Chest/abdominal/pelvic contrast-enhanced CT or integrated whole body PET-CT” was clarified as, “(≤T2 or large cell transformed or folliculotropic MF, or with palpable adenopathy or abnormal laboratory studies).”

MFSS-2
- TNMB table:
  - For Skin, “T2a” and “T2b” were added to the table.

MFSS-6
- Footnote “v” was revised from, “Skin-directed therapies are for patch or plaque lesions and not for tumor lesions” to “RT is preferred for tumor lesions.”

MFSS-A 1 of 4
- Skin-directed Therapies:
  - "Carmustine" was removed from topical chemotherapy.
- Systemic Therapies
  - Category B
    - The first-line regimens are now listed in alphabetical order.
    - “Brentuximab vedotin” was added to first-line therapies.
    - “Low-dose pralatrexate” was moved from second-line to first-line therapies.
  - Category C
    - The regimens are now listed in alphabetical order.
    - “Brentuximab vedotin” was added.

MFSS-B
- Supportive Care for MF/SS
  - Infections, “Cutaneous viral infections: High-risk for skin dissemination of localized viral infections (HSV/VZV)” was added.