Modification and Implementation of NCCN Guidelines™ on Lymphomas in the Middle East and North Africa Region

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Abstract
In the Middle East and North Africa (MENA) region, cancer has many epidemiologic and clinical features that are different from those in the rest of the world. Additionally, the region has a relatively young population and large disparities in the availability of resources at diagnostic and treatment levels. A critical need exists for regional guidelines on cancer care, including those for lymphoid malignancies. A panel of lymphoma experts from MENA reviewed the 2009 version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Non-Hodgkin’s Lymphoma and Hodgkin Lymphoma and suggested modifications for the region that were discussed with the United States NCCN Lymphoma Panels. This article presents the consensus recommendations. (J NCCN 2010;8[Suppl 3]:S29–S35)

Overview
In the Middle East and North Africa (MENA) region, cancer has many epidemiologic and clinical features that are different from those in the rest of the world. Additionally, the region has a relatively young population and large disparities in the availability of resources at diagnostic and treatment levels. A critical need exists for regional guidelines on cancer care, including those for lymphoid malignancies. A panel of lymphoma experts from MENA reviewed the 2009 version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Non-Hodgkin’s Lymphoma and the 2008 version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Hodgkin Lymphoma (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org) and suggested...
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Modifications for the region that were discussed with the United States NCCN Non-Hodgkin’s Lymphoma Panel. This article presents the consensus recommendations.

For Hodgkin lymphoma, if PET-CT scan is not available, Gallium scan or biopsy is recommended to evaluate for residual disease. In mantle cell lymphoma, rituximab and a high-dose cytarabine-containing regimen such as DHAP (dexamethasone, cisplatin, cytarabine) were added to the first-line options. In diffuse large B-cell lymphoma, the dose-dense, dense-intense R-ACVBP (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) regimen was added as an acceptable alternative to R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in patients younger than 60 years. In Burkitt’s lymphoma, the LMB (B-cell non-Hodgkin’s lymphoma and B-cell acute lymphoblastic leukemia) protocol was added as an acceptable alternative and rituximab use was recommended for all CD20-positive tumors. In cutaneous lymphomas, human T-cell lymphotropic virus type 1 (HTLV-1) serology was recommended, particularly for patients from endemic areas. Finally, the panel formulated new recommendations for the diagnosis, workup, and management of HTLV-1–associated adult T-cell leukemia/lymphoma (ATL). In the acute, chronic, and smoldering forms of ATL, antiviral therapy using the combination of zidovudine and interferon (IFN)-α is recommended. Allogeneic hematopoietic stem cell transplantation (HSCT) is recommended in patients with acute ATL who do not experience a complete remission. In ATL lymphoma, first-line chemotherapy followed by allogeneic HSCT is recommended.

In the MENA region, these suggested modifications should encourage the use of the NCCN guidelines for treating patients with lymphoma. At the global level, they represent an important addition to the NCCN guidelines by providing recommendations for the management of patients with ATL.

Background

Malignant lymphomas constitute a sizeable percentage of human cancers, and recent epidemiologic data suggest a worldwide increase in incidence (approximately 30% in the past 5 years), which may be caused by environmental factors, including increased pesticide use, and the emergence of infectious diseases, such as hepatitis C virus infections. These malignant lymphomas represent a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment. Most non-Hodgkin lymphoma (NHL) cases are of B-cell origin; however, histologic subtypes may vary in different parts of the world.

Prognosis depends on histologic type, stage, age, and treatment. In addition, tumor environment (e.g., immune and stromal infiltration), presence of infectious agents associated with lymphomagenesis, and molecular events involved in cell proliferation, differentiation, and apoptosis are emerging as new prognostic factors that eventually may be used for targeted therapies. Hodgkin lymphoma is characterized by a very good prognosis and a significant cure rate with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)-type chemotherapy. However, targeted therapy either alone or in combination with chemotherapy has significantly improved the prognosis of NHL of B-cell origin, particularly with the use of rituximab, an anti-CD20 monoclonal antibody.

Diffuse large B-cell lymphoma (DLBCL) is a distinct histologic type within B-cell NHL characterized by large tumor cells and aggressive clinical behavior. This subtype accounts for approximately 30% to 40% of adult NHL.

Regional specificities in the incidence of lymphomas have been reported with a significantly lower incidence of follicular lymphoma and chronic lymphocytic leukemia, and a significantly higher incidence of T-cell lymphomas in Asian countries compared with Europe and North America. A high incidence of Epstein-Barr virus–associated lymphomas has been reported in some Middle East countries. In addition, HTLV-1–associated ATL is endemic in some Middle East regions.

Finally, management of malignant lymphomas in developing countries is variable and largely depends on the availability of diagnostic and therapeutic resources, such as immunohistochemistry and molecular techniques, PET-CT scan, and expensive targeted therapies.

Methods

The NCCN–MENA project was launched during a preparatory meeting held in Abu Dhabi, United Arab Emirates on November 9, 2008, involving NCCN members and chairpersons of the different
guidelines panels. The goal was to adapt the NCCN guidelines to the region. The chair of the NCCN Lymphoma Panel, in consultation with the chairmen of the NCCN–MENA project and chairpersons of other groups, nominated lymphoma experts from multiple specialties, including hematology, medical oncology, radiation oncology, pathology, and diagnostic radiology, to join the NCCN–MENA guideline committee. These individuals were contacted by e-mail and agreed to participate. All members were e-mailed the 2008 version of the NCCN Guidelines on Non-Hodgkin's Lymphomas and the 2009 version of the NCCN Guidelines on Hodgkin Lymphoma and asked to communicate their suggested modifications. Several members sent their suggested modifications to the whole group.

The regional lymphoma group met in Beirut, Lebanon on February 21, 2009, to discuss the suggested modifications. Consensus recommendations were made, including specific modifications to the existing NCCN recommendations and new recommendations for ATL management because none were present in the 2009 version of the NCCN Guidelines on Non-Hodgkin's Lymphomas. The chair compiled these modifications and forwarded them to the chair of the NCCN Non-Hodgkin's Lymphomas Panel in the United States, and then the comments of the NCCN panel were e-mailed to the MENA lymphoma committee. Subsequently suggested MENA modifications were presented at the Abu Dhabi meeting in April 2009; consensus recommendations were then established at a special lymphoma committee meeting attended by several MENA lymphoma committee members and the chair of the NCCN panel. These recommendations were then discussed and finalized by the NCCN panel in June 2009.

**Hodgkin Lymphoma**

**Background**

The current NCCN treatment algorithm for Hodgkin lymphoma is based on PET-CT findings. However, this modality is not available or accessible everywhere. A small survey of the groups' practices showed that Gallium scan is more widely available and accessible in the MENA region. Imaging with Gallium requires several days, but there is no need to wait after the end of treatment. A baseline scan is also required.

Some studies indicate no statistical difference between the imaging methods. However, most studies indicate that PET is superior to Gallium scan in terms of sensitivity for activity and site detection, and also has a slightly higher specificity.

**Suggested Modification**

- If PET-CT is not available, Gallium scan is recommended.
- If Gallium scan is not available, a biopsy of the residual disease is recommended.
- If Gallium scan is positive, a biopsy is recommended.
- If Gallium scan is negative, the group recommends following the NCCN guidelines for negative PET-CT scan.

**Mantle Cell Lymphoma**

**Background**

Several reports show that high-dose cytarabine is an effective chemotherapeutic agent in mantle cell lymphoma. For example, the protocol involving R-DHAP (dexamethasone, cisplatin, high-dose cytarabine, rituximab) followed by autologous stem cell transplant (ASCT) for previously untreated younger patients (< 65 years) is a very affordable and rather effective regimen, with 3-year overall and event-free survival rates of 75% and 76%, respectively, based on an intent-to-treat analysis.

**Suggested Modification**

The group recommended that suggested first-line treatment regimens include a rituximab and high-dose cytarabine-containing regimen, such as DHAP, with a corresponding footnote indicating that high-dose chemotherapy and ASCT should be given after high-dose cytarabine.

**DLBCL**

**Background**

Multiple studies have shown that advances in treatment can improve the outcome of patients with DLBCL, and that the standard CHOP regimen is not sufficient as first-line chemotherapy to cure many patients. The first improvement was reported in 2 randomized studies, which showed the superiority of a dose-dense and -intense regimen, ACVBP
Numerous small phase II studies using zidovudine (AZT) and IFN-α have shown responses in patients with ATL. High doses of both agents were used: 6 to 9 million units of IFN-α in combination with daily divided AZT doses of 800 to 1000 mg/d. However, only patients with wild-type p53 and low IFN regulatory factor 4 expression seem to exhibit long-term responses to AZT/IFN therapy.

The results of a recent worldwide meta-analysis on the use of AZT/IFN for treating ATL indicate a significant survival advantage in acute, chronic, and smoldering-type ATL, but not in lymphoma ATL. The recently published proposal from the International Consensus Meeting recommended a strategy for treating ATL.

Suggested Modification:
The group recommended adding R-ACVBP as an acceptable alternative to R-CHOP.

Burkitt’s Lymphoma

Background
Excellent results are reported in young adults treated with the pediatric LMB protocol. The second improvement was the increased survival achieved with the addition of rituximab to combination chemotherapy. Furthermore, rituximab significantly improves outcome in patients with CD20-positive Burkitt’s lymphoma.

Suggested Modification
The group suggested that the LMB protocol be added as an acceptable alternative to the current NCCN Guidelines for Burkitt’s Lymphoma (CODOX-M or HyperCVAD), and that rituximab use be considered for all tumors that are CD20-positive.

T-Cell Lymphomas

ATL

Background: ATL is an aggressive malignancy of mature activated CD4-positive CD25-positive T cells associated with a retrovirus-designated HTLV-I. Endemic areas include Japan, the Caribbean, intertropical Africa, Brazil, Eastern Europe (Romania), and the Middle East (particularly Iran). The diversity in clinical features and prognosis of patients with this disease has led to its subclassification into 4 categories: acute, lymphoma, chronic, and smoldering types (Table 1). The chronic and smoldering subtypes are considered indolent, but eventually have poor long-term survival.

Patients with aggressive ATL (acute and lymphoma types) generally have a very poor prognosis because of multidrug resistance of malignant cells, a large tumor burden with multiorgan failure, hypercalcemia, or frequent infectious complications from a profound T-cell immunodeficiency. Numerous small phase II studies using zidovudine (AZT) and IFN-α have shown responses in patients with ATL. High doses of both agents were used: 6 to 9 million units of IFN-α in combination with daily divided AZT doses of 800 to 1000 mg/d. However, only patients with wild-type p53 and low IFN regulatory factor 4 expression seem to exhibit long-term responses to AZT/IFN therapy.

The results of a recent worldwide meta-analysis on the use of AZT/IFN for treating ATL indicate a significant survival advantage in acute, chronic, and smoldering-type ATL, but not in lymphoma ATL. The recently published proposal from the International Consensus Meeting recommended a strategy for treating ATL.

Suggested Modification:
Diagnosis: In all patients with leukemic manifestations, ATL is usually diagnosed based on the presence of 5% or more abnormal T lymphocytes in peripheral blood according to morphology and flow cytometry. In those without leukemic manifestations, it is diagnosed based on a finding of T-cell lymphoma on biopsy of involved organs. Additionally, HTLV-1 seropositivity is mandatory for ATL diagnosis. Clonal integration of HTLV-1 provirus should be performed in most cases and is mandatory in atypical cases.

Workup: The group recommended that workup for ATL include the following:

- CBC and blood smear: lymphocytosis (absolute lymphocyte count > 4000) in acute and chronic subtypes. Typical ATL cells (“flower cells”) have markedly polylobated nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm, but multiple morphologic variations can be encountered.
- Flow cytometry on peripheral blood: mature T-cell phenotype. Minimum panel: CD3, CD4, CD7, CD8, and CD25. Usually CD4-positive cells with expression of CD2, CD5, CD25, CD45R0, CD29, T-cell receptor–αβ, and HLA-DR. Most cases are CD7-negative and CD26-negative with low CD3 expression. Rare cases are CD8-positive or CD4/CD8-double positive or CD4/CD8-double negative.
- HTLV-I serology: positive (enzyme-linked immunosorbent assay and Western blot).
- Molecular analysis: monoclonal integration of
HTLV-I provirus (Southern blot or inverted polymerase chain reaction).

- Bone marrow aspirate and biopsy: generally not required to make the diagnosis. However, bone marrow involvement is an independent poor prognostic factor.
- Radiologic imaging: CT scans of neck, thorax, abdomen, and pelvis. Skeletal survey in symptomatic patients.
- Gastrointestinal evaluation: upper gastrointestinal endoscopy (frequent gastrointestinal involvement).
- Central nervous system evaluation: CT scan, MRI, and/or lumbar puncture in all patients with acute or lymphoma subtypes or in those with neurologic manifestations.
- Biopsy of lymph nodes (excisional), skin biopsy, gastrointestinal tract biopsy, or bone marrow biopsy is required if the diagnosis is not established based on molecular assay of peripheral blood (for histology and molecular analyses of HTLV-I provirus integration), or to rule out an underlying infection (e.g., tuberculosis, histoplasmosis, toxoplasmosis).
- Chemistry: electrolyte, blood urea nitrogen, creatinine, serum calcium, and serum lactate dehydrogenase (LDH) levels.
- Stool examination for parasites.

**Treatment of Chronic/Smoldering ATL:** The group recommends treatment for all patients with chronic/smoldering ATL. Recent results from a Japanese study show poor outcome for patients treated with a “watch and wait” strategy or chemotherapy. The group recommended that treatment include the following:

- Initial therapy outside clinical trials: AZT (1 g/d orally) and IFN-α (6–10 million units per day). A recent worldwide meta-analysis showed this regimen resulted in 100% long-term survival. A recent worldwide meta-analysis showed this regimen resulted in 100% long-term survival.
- Response evaluation: complete remission is defined by normalization of lymphocytosis (if present) and LDH level (if elevated), with disappearance of all clinical manifestations (particularly skin involvement and lymphadenopathy). However, persistence of fewer than 5% flower cells on peripheral smear is allowed.
- Almost all patients with chronic or smoldering ATL should experience response to AZT/IFN. Outside clinical trials, treatment should never be interrupted in these patients. Response is usually obtained within 1 to 2 months. If no response is seen at 2 months, treatment should be discontinued. In patients who experience progression with life-threatening manifestations, treatment can be discontinued before 2 months.
- Very few patients with chronic/smoldering ATL will not experience response or will experience progression after AZT/IFN. For these patients, chemotherapy is recommended (CHOP is the most used regimen, although one randomized study showed that Japanese LSG15 [vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); doxorubicin, ranimustine, and prednisone (AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP)] is superior to CHOP).

### Table 1  Adult T-Cell Leukemia/Lymphoma Subtype According to Shimoyama Classification

<table>
<thead>
<tr>
<th></th>
<th>Healthy Carrier</th>
<th>Smoldering ATL</th>
<th>Chronic ATL</th>
<th>Acute ATL</th>
<th>ATL Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTLV-I serology</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clonal integration of provirus (blood)</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>Normal</td>
<td>Normal</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Normal</td>
</tr>
<tr>
<td>Abnormal cells</td>
<td>&lt; 5%</td>
<td>&gt; 5%</td>
<td>&gt; 5%</td>
<td>&gt; 5%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LDH level</td>
<td>Normal</td>
<td>&lt; 1.5 N</td>
<td>&lt; 2 N</td>
<td>&gt; 2 N</td>
<td>&gt; 2 N</td>
</tr>
<tr>
<td>Skin or lung involvement</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bone marrow or spleen involvement</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bone, gastrointestinal, or central nervous system involvement</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: ATL, adult T-cell leukemia/lymphoma; HTLV-1, human T-cell lymphotropic virus type 1; LDH, lactate dehydrogenase.
Treatment of Acute ATL:
- Recommended initial therapy outside clinical trials: AZT (1g/d orally) and IFN-α (6–10 million units per day). This strategy is associated with an improved survival rate compared with first-line chemotherapy in worldwide meta-analysis. High doses of both agents are needed for at least 1 month. Dose reduction for hematotoxicity is allowed starting from month 2.
- Response evaluation: complete remission is defined by normalization of lymphocytosis (if present) and the LDH level (if elevated), with disappearance of all clinical manifestations and tumor sites. However, persistence of less than 5% flower cells on peripheral smear is allowed.
- Outside clinical trials, treatment should never be interrupted in patients experiencing response. Response is obtained within 1 to 2 months. If no response is achieved at 2 months, AZT/IFN should be discontinued. In patients experiencing progression with life-threatening manifestations, treatment can be discontinued before 2 months.
- Alternative first-line option and for patients who do not experience respond or will experience progression after AZT/IFN: inclusion in clinical trials or chemotherapy (CHOP is the most used regimen, although one randomized study showed that Japanese LSG15 [VCAP, AMP, and VECP] is superior to CHOP). Data are weak for monoclonal antibodies (anti-CD52 or -CD25).
- Young patients with an HLA–identical donor should be referred for allogeneic HSCT (myeloablative or reduced-intensity conditioning).
- Antimicrobial prophylaxis: trimethoprim-sulfamethoxazole (Bactrim) and strongyloidosis prophylaxis is recommended.
- Central nervous system prophylaxis: intrathecal chemotherapy is recommended (methotrexate, cytarabine, and corticosteroids).

Cutaneous T-Cell Lymphomas

Background
Many patients with smoldering ATL can be misdiagnosed with mycosis fungoides or Sézary syndrome if HTLV-I serology is not requested.

Suggested modification
- The group recommends including HTLV-I serology as part of the workup, particularly if the patient is from an endemic area.

Conclusions
In the MENA region, these suggested modifications should encourage the use of the NCCN guidelines for treating patients with lymphoma. At the global level, they represent an important addition to the NCCN guidelines by providing recommendations for managing patients with ATL.

References


