Fundamentals of the Management of Non-Hodgkin Lymphoma

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SUMMARY

The incidence of Non-Hodgkin's lymphomas (NHL) is rising worldwide and if not adequately treated carries a high mortality rate. The pattern and frequency of NHL vary in different populations and geographical regions. It has considerable biologic and clinical heterogeneity and a definitive diagnosis can be made only after histopathogical examination. The histology and the extent of the lymphoma are the major determinants of optimal therapeutic regimen and treatment outcome. Additionally, the overall treatment strategies should be tailored according to medical status and preference of the patient.

A holistic approach provided by a multi-disciplinary team of health care professionals is the cornerstone of ensuring successful treatment outcome. Importantly, therapy should be expedited and where possible performed in experienced centers. Patients achieving remission would require long term monitoring for disease recurrence and late effects of cytotoxic chemotherapy and radiotherapy. Hence, clinicians should have a fundamental understanding in the biology and the principles of treatment of NHL.

This review provides an evidence-based and systematic approach in designing therapeutic strategies for individual patients with newly diagnosed and relapsed NHL focusing on the common types of NHL with particular reference to the current practice within the local settings. The role of standard and novel therapeutic modalities in treatment will be summarized.

KEY WORDS:
Non-Hodgkin Lymphoma, Diffuse large B cell lymphoma, Follicular lymphoma, Rituximab

INTRODUCTION

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) lymphocytes. B-cell lymphomas accounts for 80-90% of the cases with 15-20% being T-cell lymphomas. NK lymphomas are very rare[1].

NHL is the fifth leading type of new cancer cases among men and women, accounting for 4-5% of new cancer cases and 3% of cancer- deaths among men and the sixth among women in the United States[1]. In Malaysia, NHL is the third commonest cancer (7.4%) in male and tenth (2%) in female aged 15-49 years, and tenth (2-4%) in male and 14th (1-2%) female aged above 50[2].

The pattern and frequency of NHL vary in different populations and geographical regions. Compared to the West, follicular NHL is less common and T- and NK-cell NHL are more common in Asia. Additionally, the incidence of primary extranodal lymphoma is high among Asian population, with the commonest site being the gastrointestinal tract, nasal cavity and tonsils[3]. Extranodal lymphoma is distinct from nodal NHL in many ways ranging from treatment strategies to prognosis.

Many patients with DLBCL and FL will have widespread disease at presentation and can be rapidly fatal if left untreated. Expedited and holistic care should be provided by a team of health care professionals who are experienced in treating NHL. This team may include medical oncologist, radiation oncologist, haematologist, surgeon, pathologist, oncology nurse, radiologist, and social worker.

In addition, adequate psychological and family support is vital to ensure effective delivery of treatment and to facilitate recovery from therapy. Shared decision making is recommended in all instances.

The outcome of patients with lymphoma is highly variable, and the histology of the lymphoma is the major determinants of treatment outcome and prognosis. Some patients with indolent lymphoma may remain well for many years with minimal or no therapy, whereas patients with aggressive lymphoma may succumb rapidly unless aggressive treatment is initiated promptly.

Owing to the clinical heterogeneity of NHL, individualized treatment approach is the cornerstone of ensuring successful treatment outcome. For this, several prognostic models have been used to design therapeutic trials for patients with aggressive and indolent NHL, and in the selection of appropriate treatment approaches for individual patients[4].

Currently, multiple novel agents are being developed for the treatment of NHL. Despite these major therapeutic advances, a significant proportion of patients will relapse or remain refractory to initial treatment.

This article was accepted: 2 December 2009
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On the other hand, as more patients will be cured with availability of novel therapeutic strategy, late effects of cytotoxic chemotherapy and radiotherapy among long term lymphoma survivors remain a major concern. Hence, there is an increasing emphasis on attaining long-term survival with the least acute and late toxicity from chemotherapy and RT.

This review explores the fundamental elements involved in the management of patients with NHL with particular reference to the common and pertinent queries from patients and their caregivers. The information presented herein may be used as guidelines in counseling patients to understand their disease and the treatment.

What causes NHL?

In most cases, the causes of NHL are unknown. However, it has been associated with chronic inflammatory or autoimmune diseases such as Sjögren syndrome, Hashimoto's thyroiditis and rheumatoid arthritis. Chronic infection also is associated with lymphoma pathogenesis as shown by the association between mucosa-associated lymphoid tissue (MALT) lymphomas and *Helicobacter pylori* infection[5].

Immune suppression also has been associated with an increased risk of NHL. In patients who undergo solid organ transplantation[6], the risk of lymphoma has been associated specifically with the duration of immunosuppression and with the drugs used. Furthermore, *human immunodeficiency virus* (HIV) infection has been associated with a substantially elevated risk of NHL.

What are the types of NHL?

Because there are so many types of NHL, several different systems have been developed to classify the disease. The International Working Formulation (IWF) classifies NHL into indolent/low grade, aggressive/intermediate grade or highly aggressive/high grade according to their morphology and natural histories[7].

In many centers, the histological report should give the diagnosis according to the currently internationally accepted revised REAL/WHO system[8]. This system sorts NHL into B cell, T-cell and NK-cell neoplasms based on their morphology, immunophenotype and genetic features. These features have aided in defining active treatment for specific subtypes of lymphoma.

The two most common histological disease entities are diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).

What are the clinical manifestations of NHL?

Patients with indolent lymphomas, such as follicular, marginal zone, and lymphoplasmacytic lymphoma, commonly present with slowly progressive and usually painless peripheral lymphadenopathy. Spontaneous regression of enlarged lymph nodes can occur. Primary extranodal involvement or systemic symptoms are less common at presentation but are seen more commonly as the disease advances or transforms to aggressive NHL. Bone marrow involvement in indolent lymphomas is frequent and sometimes is associated with cytopenias. Splenomegaly is seen in approximately 30% to 40% of patients, but the spleen is rarely the only site of disease involvement at presentation[9].

The clinical presentation of aggressive lymphomas, such as DLBCL, is more variable. Most patients present with lymphadenopathy; however, many present with extranodal involvement. The most common extranodal sites are the gastrointestinal (GI) tract, skin, bone marrow, sinuses, thyroid, or central nervous system (CNS). Molecular studies have indicated substantial differences between nodal and extranodal DLBCL, suggesting that both have distinct genetic origins and could arguably be regarded as different entities[10]. B-symptoms are more, occurring in approximately one third of patients. Patients with lymphoblastic lymphoma often present with an anterior mediastinal mass that is sometimes associated with superior vena cava obstruction. Burkitt lymphoma typically disseminates to the bone marrow and meninges and involves extranodal sites[9].

How is NHL diagnosed?

No effective method is available for screening patients for lymphoma, and identifying populations at high risk of lymphoma is challenging. Currently, patients are identified only after they develop lymphadenopathy or other symptoms associated with their disease.

Histology remains compulsory to establishing the diagnosis in all cases and a definitive diagnosis can be made only after biopsy specimens are reviewed by an expert haematopathologist.

Diagnosis should be made on the basis excisional lymph node or extranodal tissue biopsy providing enough material for formalin-fixed samples. Core biopsies should only be performed in patients without easily accessible lymph nodes (e.g. retroperitoneal bulk) or in patients requiring emergency treatment[11]. Fine needle aspiration alone (FNA) alone is not acceptable as a reliable for initial diagnosis of NHL[12]. For patients with intra-abdominal and retroperitoneal mass as the only sites of disease, laparoscopy has a role in establishing the diagnosis.

Immunohistochemical study is essential for differentiating the various subtypes of NHL and also to determine prognosis as these will influence the choice of therapy. It can be performed by flow cytometry and/or immunohistochemistry utilizing a minimal antibody panel (CD45, CD20 and CD3) to identify B, T or NK subtypes. The typical immunophenotype for DLBCL is CD20+, CD45+, and CD3- and FL CD20+, CD10+, bcl-2+, CD43- and CD5-. Other additional markers aid identification of subtypes, e.g. cyclin D1 for mantle cell lymphoma. Ki-67 a marker of proliferation index (PI) which is used in the histological grading of NHL, is valuable in predicting survival[13]. Overall survival (OS) was significantly reduced inpatients with high Ki-67 (high PI) compared to those lower PI[14].

Molecular cytogenetic analysis to identify the specific chromosomal translocations that are more commonly seen in particular NHL subtypes may be necessary in cases of diagnostic difficulties. Most cases (80%) of Burkitt lymphoma have a translocation of c-myc from chromosome 8 to the immunoglobulin (Ig) heavy chain region on chromosome14 [t(8;14)][15].

What investigations are required once a patient is diagnosed with NHL?

Since treatment depends substantially on the stage of the disease and medical status of the patient, a thorough initial work-up designed to identify all sites of known disease and baseline organ functions.

Initial work-up should include complete blood count, serum lactate dehydrogenase (LDH), renal/liver function tests, uric acid, computed tomography (CT) scan of the chest and abdomen as well as a screening test for human immunodeficiency virus and hepatitis B and C viruses. Cardiac function should be tested before treatment because most chemotherapy regimen include an anthracycline drug that can damage the heart. Patients amenable to curative therapy should have a bone marrow aspirate and biopsy. Bone marrow involvement is associated with significantly shorter survivals in patients with intermediate or high-grade lymphomas[16].

A diagnostic spinal tap directly combined with a first prophylactic instillation of cytarabine and/or methotrexate is indicated in high-risk patients according to international prognostic index (IPI), especially with involvement of CNS, orbital, bone marrow, testis, spine, or base of the skull. It is also indicated in the case of HIV-associated lymphoma and highly aggressive NHL[11,17].

Based on the Ann Arbor staging system (Box 1,[18]), patients are categorized into limited (Stage I, II) and advanced (Stage II, IV) disease. This system is designed based on the distribution and number of involved sites, presence or absence of extranodal involvement and constitutional symptoms.

The next step is to identify specific group of patients who are more or less likely to be cured with standard therapy. On the basis of age, tumour stage, LDH serum level, performance status, and number of sites of extranodal disease, the International Prognostic Index (IPI) distinguishes four different risk groups. The four groups had a predicted 5-year survival of: 73% (low-risk group), 51% (low–intermediate risk group), 43% (high–intermediate risk group), and 26% (high-risk group). Because younger and older patients may have different outcomes and younger patients may be considered for more aggressive therapy, an age-adjusted IPI (Box 2,[4]), for patients aged 60 years or younger also has been developed. This model identifies four risk groups with a predicted 5-year survival of: 83% (no adverse factors), 69% (one adverse factor), 46% (two adverse factors), and 32% (three adverse risk factors).

The IPI was designed for aggressive lymphoma and may not clearly identify patients with indolent lymphoma who are at high risk; thus, a new prognostic factor model has been devised for FL. The Follicular Lymphoma International Prognostic Index (FLIPI)[19] uses the patient's age (>60 vs ≤60 years), Ann Arbor stage (III or IV vs I or II), haemoglobin level (<12 g/dL vs ≥12 g/dL), number of nodal areas (>4 vs ≤4), and serum LDH level. The FLIPI is predictive of overall survival[20], hence may be used to identify patients that may benefit from more aggressive therapy.

BOX 1

Cotswolds Modification of Ann Arbor Staging System
Stage Area of Involvement

I	Single lymph node group
II	Multiple lymph node groups on same side of diaphragm
III	Multiple lymph node groups on both sides of diaphragm
IV	Multiple extranodal sites or lymph nodes and extranodal disease
X	Bulk > 10 cm
E	Extranodal extension or single isolated site of extranodal disease
A/B	B symptoms: weight loss > 10%, fever, drenching night sweats

Adapted from reference no. 18

BOX 2

INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:
- Age > 60 years
- Serum LDH > 1 x normal
- Performance status 2-4
- Stage III or IV
- Extranodal involvement > 1 site

INTERNATIONAL INDEX, ALL PATIENTS:

• Low	0 or 1
• Low intermediate	2
• High intermediate	3
• High	4 or 5

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤ 60 YEARS :
- Stage III or IV
- Serum LDH > 1 x normal
- Performance status 2-4

INTERNATIONAL INDEX, PATIENTS ≤ 60 YEARS:

• Low	0
• Low/intermediate	1
• High/intermediate	2
• High	3

Adapted from reference no. 4

Learning points

1. Core needle biopsy is discouraged unless the clinical situation dictates that this is the only safe means of obtaining diagnostic tissue.
2. Fine needle aspiration alone is inappropriate for an initial diagnosis of NHL, though it may be sufficient to establish relapse.
3. The diagnosis of NHL should be made based on adequate sample by an experienced pathologist.
4. Studies of immunophenotype and molecular genetics are essential to refine the diagnosis.
5. Key elements in the determining the optimal therapeutic strategies of NHL are the tumour histology and stage and patient's prognostic index.
6. PET scan is useful in evaluating residual masses following chemotherapy for DLBCL.
7. Rituximab-CHOP is considered the standard of care for DLBCL.
8. Autologous HSCT is an established treatment in relapse lymphoma.

What are the treatment options and outcome of treatment in patients with newly diagnosed NHL?

Not all patients with lymphoma require immediate treatment upon diagnosis. The decision to initiate therapy depends primarily on the histology NHL. Since the natural course of indolent NHL is characterized by spontaneous regressions in 15–20% of cases, chemotherapy should be initiated only upon the occurrence of symptoms including B symptoms, haematopoietic impairment, bulky disease or rapid lymphoma progression[21]. In contrast, treatment should not be delayed in patients diagnosed with aggressive or advanced stage lymphoma.

Apart from the histology, the overall treatment strategies should be tailored according to tumour stage and patient's baseline prognostic index and preference.

The patient should be involved in the decision process from the start, which has to balance the chance of cure against the risks of treatment related mortality. When cure is the aim, it is desirable to treat patients with the least toxic therapy that will achieve a durable complete remission. These include limiting the number of chemotherapy cycles and restricting radiotherapy to those most likely to benefit from it.

B - cell NHL

Treatment strategies for patients with DLBCL differ between patients with limited or advanced disease and the presence or absence of risk factors[22,23]. Patients of all ages with stage I-II DLBCL and no adverse prognostic factors (non-bulky disease and IPI prognostic index equal to 0) should receive abbreviated (three – four cycles) chemotherapy with an anthracycline-containing regimen plus involved field RT (35-40 Gy) or a full course (six – eight cycles) of chemotherapy alone. Patients with stage I-II disease and at least one adverse prognostic factor (bulky disease, elevated LDH, performance status ECOG >1) should be treated according to the recommendations for stage III-IV disease. These patients should receive six to eight cycles of chemotherapy.

Standard first-line chemotherapy for all patients with CD20+ DLBCL is cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) combined with rituximab (R) given every 21 days. This results in complete remission (CR) rate of 75%-80% and a 3-5-year progression-free survival (PFS) of 50%-80% [24,25]. The addition of rituximab to CHOP (R-CHOP) has been the most significant advance in treatment of DLBCL with an improvement in PFS and OS by 15%- 20% over CHOP chemotherapy alone[24-26].

Patients with symptomatic stage I-II FL can be treated with radiotherapy alone while patients with stage III-IV or grade 3 histology should be treated with chemotherapy as for DLBCL[27,28]. Highly aggressive NHL such as Burkitt's lymphoma and lymphoblastic lymphoma has generally been treated with acute lymphoblastic leukaemia (ALL)-like regimens that include intrathecal chemotherapy due to the propensity for CNS relapse[29].

T-cell NHL

The management of peripheral T-cell lymphomas (PTCL) has not been well-defined, but therapy should be based on the stage of disease and the specific immunopathologic disease entity. However, the complete response rate, with the exception of ALK+ anaplastic large cell lymphoma, is lower than in B-cell lymphomas treated with the same chemotherapy combination[30]. Because of a paucity of comparative trials, there is little evidence that any particular combination chemotherapy is superior to the others. Therefore, clinical trials are the preferred treatment option for all patients with PTCL.

HIV-associated lymphoma

Optimal management of HIV-associated lymphoma (HAL) is not established. CHOP given with concomitant HAART[31] or EPOCH regimen (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) without HAART[32] have proven to be effective and tolerable in patients with HAL. The NCCN guidelines recommend full dose chemotherapy with growth factor support and prophylactic therapy with intrathecal chemotherapy[33]. Rituximab appears to increase the risk of neutropenia and infection and there is no net benefit in patients with HAL[34]. The omission of rituximab is strongly suggested for DLBCL patients with CD4 counts of less than 50 due to the higher risk of infectious toxicities[35].

Ancillary therapy and Care

Other than tumor specific therapies, good supportive care is essential in ensuring successful treatment outcome. In cases with high tumor load, special precautions (e.g. corticosteroid pre-phase and alkaline diuresis) are required to avoid tumor lysis syndrome. Anti-emetics and anti-infective measures should be initiated prior to commencement of chemotherapy. Antiviral prophylaxis is beneficial in preventing hepatitis B virus reactivation. History of febrile neutropenia following chemotherapy justifies prophylactic use of haematopoietic growth factors in patients treated with curative intent. Because treatment may affect fertility, this issue including sperm banking needs to be addressed if the patient wants to have a family.

Following chemotherapy, the patients should be monitored closely for the development of infection and bleeding associated with myelosuppression. Empiric antibiotic therapy and growth factors are important measures in the treatment of febrile neutropenia.

How would response be determined?
Abnormal radiological tests at baseline should be repeated after mid-cycle and last cycle of treatment. Bone marrow aspirate/biopsy should be repeated only at the end of treatment if initially involved. CT is the most commonly used imaging modality for response assessment but CT has limitations in differentiating between viable tumour, necrosis and fibrosis in residual masses. By contrast PET scan is useful in determining the etiology of posttherapy residual masses in aggressive NHL[36].

PET scans are particularly informative for response evaluation after treatment because they can distinguish residual fibrotic masses from masses containing viable tumor[37]. Early interim PET correlates with progression-free survival and overall survival[38]. For these reasons, PET/CT is rapidly replacing CT scan for treatment response assessment and has now been incorporated into the response criteria.

Response to treatment is categorized as CR, partial remission (PR), stable disease (SD) and relapsed disease or progressive disease (PD) based on the reduction in the size of the enlarged lymph node and the extent of bone marrow involvement[39]. Patients with insufficient or lack of response to initial therapy should be evaluated for early salvage regimens.

How should patients who achieved complete remission be monitored?
Clinical evaluation should be performed every 3 months for 1 year, every 6 months for 2 more years and then once a year with special attention to development of secondary cancers including leukaemia, and thyroid and breast carcinomas[11,21].

After having received chest irradiation at premenopausal age, especially at an age <25 years, women should be screened for secondary breast cancers clinically and, after the age of 40 years, by mammography. Evaluation of thyroid function (thyroid-stimulating hormone) in patients with irradiation to the neck at 1, 2, and 5 years[11,21].

Full blood counts and serum LDH at 3, 6, 12 and 24 months, then as required for evaluation of suspicious clinical findings suggestive of disease recurrence. Minimal adequate radiological examinations at 6, 12 and 24 months after end of treatment by CT scan are indicated.

Will the cancer recurs (relapse) and what should be done if the cancer recurs?
Despite recent therapeutic advances, up to 50% of patients relapse after initial chemoimmunotherapy[40]. A repeat biopsy is strongly recommended, and is mandatory in relapses > 12 months after the initial diagnosis, in order to rule out a secondary transformation into aggressive lymphoma from low grade NHL and also to ensure CD20 positivity.

Patients still amenable to curative therapy should have the same work-up as at the first presentation. The cumulative dose of anthracyclines used in first-line therapy has to be specified. If further anthracyclines are to be used, echocardiography for quantification of the ejection fraction should be done.

What are the treatment options in patients with relapsed NHL?
To date, the standard of care in the management of relapsed/refractory DLBCL is salvage chemotherapy followed by an autologous haematopoietic stem cell transplantation (HSCT) for those with chemotherapy-sensitive disease. Event-free survival (EFS) and OS at 5 years in the transplant arm were 46% and 53%, respectively, compared with 12% and 32% in the chemotherapy alone arm[41,42].

Currently, there is no standard salvage chemotherapy regimen. The choice of salvage treatment depends on efficacy of prior regimens. In early relapses (<12 months), a non-cross resistant scheme should be preferred. Combining rituximab with salvage therapy clearly suggest superior response and disease-free survival over chemotherapy alone [II, A] in relapse DLBCL. Any of the published salvage regimens such as R-DHAP, R-ICE, etc. may be adequate until results of comparative trials are known[43,44]. The most frequently used high dose regimen locally is BEAM (carmustine, etoposide, cytosine–arabinoside and melphalan). Patients not suitable for high-dose therapy may be treated with the same or other salvage regimens (e.g. R-IMVP16, R-GEMOX, etc.) and may be combined with involved-field radiotherapy[45]. Radioimmunotherapy (RIT) with [^{131}I]-tositumumab and ^{90}Y-ibritumomab tiuxetan is an alternate treatment option for relapsed, refractory or histologically transformed FL[46].

What is the role of haematopoietic stem cell transplantation (HSCT)?
HSCT is recommended in patients with relapsed NHL. HSCT currently does not have a well-defined role in the primary therapy for aggressive lymphomas but may be considered for high-risk patients who achieve a CR to initial conventional chemotherapy[47]. However, the late effects of transplantation need to be considered because the risk of myelodysplastic syndrome and acute myeloid leukaemia is significant[48]. Because of the poor response rates and outcomes reported to date, autologous HSCT is not recommended in primary refractory or relapsed aggressive NHL not responding to salvage chemotherapy[49]. Alternative treatment strategies are required in these cases, and, wherever possible, patients should be enrolled in clinical trials assessing new treatment regimens and novel therapeutic agents.

Allogeneic HSCT is potentially curative due to its graft versus lymphoma effect, hence should be considered in younger patients with relapsed disease or highly aggressive lymphomas[50,51]. However, the benefits of lower relapse rates are abrogated by higher treatment-related mortality[52,53]. The use of nonmyeloablative or reduced-intensity allogeneic transplants has significantly decreased the early treatment related mortality and can increased the number of patients eligible for allogeneic HSCT[54-55].

Recent efforts to improve the outcome of HSCT in NHL by reducing relapse include the addition of radio-immunoconjugates to conditioning regimens and the use of rituximab for ''in vivo purging'' around the time of stem cell harvesting and also as adjuvant therapy after SCT[56-58].

What is the role of radiotherapy?
Radiation therapy is now used infrequently as the sole curative therapy in NHL except in limited stage follicular FL[27]. Consolidative radiotherapy is often used to initial bulky sites and in residual disease after completion of systemic chemotherapy. Radiotherapy may be used as palliation of symptoms in patients not suitable for systemic therapy.

What is the role of surgery?
Surgery is useful only in selected situations, most commonly to establish a diagnosis by obtaining a biopsy specimen. Because lymphoma is a systemic illness, resection of the sites of disease is used only in selected situations. Surgery may be particularly useful in primary GI lymphomas when the disease is localized or when there is a risk of perforation[59]. Orchiectomy is commonly the initial treatment for patients with testicular lymphoma[60].

CONCLUSION

The accurate documentation of the pathologic diagnosis, the anatomic extent of tumour, patient's individual prognostic index and the response to therapy are of paramount importance in the management of lymphoma. A personalized and holistic approach provided by a highly experienced team of health care professionals is the cornerstone of ensuring successful treatment outcome.

Recent therapeutic advances including the use of monoclonal-antibody based therapy and the more widespread use of HSCT have increased cure rates of patients with NHL. Enhancements in the understanding of the pathogenesis and biology of lymphoma have led to a continual development of targeted therapies for this disease. Molecular profiling of tumors has allowed the prognosis to be determined more accurately and has potentially identified new targets for treatment. New monoclonal antibodies against a wide range of T-cell and B-cell surface markers are in clinical development.

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Continuing Medical Education

MCQ: A-B-C in the Management of Non-Hodgkin Lymphoma

1. The following are true regarding the subtypes of NHL:
a. T-cell lymphomas is the commonest histological subtype;
b. Follicular NHL is the commonest type of NHL in Malaysia;
c. NK cell lymphoma is more common in Asian than in Western population;
d. Epstein-Barr virus infection is associated with development of Burkitt's lymphoma;
e. Helicobacter pylori infection is associated with mucosa-associated lymphoid tissue (MALT) lymphomas.

2. Poor prognostic factors in NHL include:
a. Age above 60 years;
b. Female gender;
c. A high LDH serum level;
d. Multiple extranodal sites;
e. Hepatitis B carrier state.

3. The following are routinely performed to determine the Ann Arbor clinical staging of lymphoma:
a. Chest radiograph;
b. Bone marrow aspirate and trephine biopsy;
c. Lumbar puncture;
d. LDH serum level;
e. HIV serology.

4. The following are true regarding the treatment of newly diagnosed NHL:
a. All patients with indolent lymphoma require immediate treatment upon diagnosis;
b. Intrathecal chemotherapy is indicated in lymphoma involving the testes;
c. Radiotherapy is the standard treatment in limited stage follicular lymphoma;
d. Response rates in patients with T-cell lymphomas is lower than in B-cell lymphomas treated with the same chemotherapy regimen;
e. R-CHOP chemotherapy is the treatment of choice in patients with lymphoblastic lymphoma.

5. The following are true regarding the treatment of relapsed NHL:
a. Less than 10% of patients with DLBL relapse after initial chemoimmunotherapy;
b. A repeat biopsy is strongly recommended in relapses occurring within the first year after the initial diagnosis;
c. Autologous stem cell transplantation is currently the standard treatment for patient with chemosensitive relapse;
d. Allogeneic SCT is associated with a lower relapse rate compared to autologous SCT;
e. Radioimmunotherapy is a treatment option in patients with relapse follicular lymphoma.