Advances in Management of Lymphoma

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Introduction

The incidence of lymphoma has risen rapidly worldwide, especially in the well developed countries. In Hong Kong, it is one of the top ten commonest cancers with over 650 new cases seen every year. Over 90% of the patients have non-Hodgkin’s lymphoma. Compared with the western populations, we have a much lower incidence of Hodgkin’s lymphoma and low grade non-Hodgkin’s lymphoma, such as follicular lymphoma and small lymphocytic lymphoma. Most cases seen in Hong Kong are aggressive high grade non-Hodgkin’s lymphoma. There also appears to be a higher incidence of T-cell or natural killer cell lymphoma in Hong Kong.1-4

Although most lymphoma patients present with lymphadenopathy, an extra-nodal primary, such as stomach, nasal cavity and skin are not uncommon. (Figure 1) Lymphoma may practically arise from almost any organ or tissue of the body. A high index of suspicion is essential for early diagnosis.5, 6 Common metastatic extra-nodal sites include the spleen, liver, bone marrow, pleura and the central nervous system. Systemic symptoms such as fever, night sweat and weight loss may also be present.

Diagnosis

A well performed tissue biopsy is essential for precise diagnosis. It cannot be replaced by radiological imaging or a fine needle aspiration. Computerised tomography, Magnetic Resonance Imaging or Positron Emission Tomography may help to assess the extent of the involvement and guide the biopsy. A properly performed fine needle aspiration together with a flow cytometric study may strongly suggest a diagnosis of lymphoma, a tissue biopsy specimen if technically feasible however is always preferred for proper diagnosis and classification.

The WHO classification for lymphoma is now widely used. (Table 1-3) This new classification takes into consideration the clinical, morphological, immunological, cytogenetic and molecular genetic features. With more understanding of the pathological processes, the classification is evolving.7 A new version of the classification is expected to be available in 2008.

Assessment

The tissue biopsy specimens should preferably be reviewed by experienced pathologists familiar with lymphoma. Accurate diagnosis and precise histological classification are essential for optimal management of the patients. The extent of the lymphoma involvement can be assessed by modern imaging (CT, MRI and PET).8 Other important prognostic facts should also be determined. An international prognostic index, incorporating age, performance status, Ann Arbor staging, number of extra-lymphatic sites and serum lactate dehydrogenase level, has been used to predict prognosis of patients with diffuse large B-cell lymphoma.9 Other prognostic indices have been formulated for other histological subtypes, such as follicular lymphoma.10

The patients should also be assessed for any other concomitant illnesses. All lymphoma patients must have their hepatitis B, hepatitis C and HIV status determined. Treatment of the lymphoma may reactivate pre-existing infections. In Hong Kong, 10% of the patients are hepatitis B carriers with a positive serum hepatitis B surface antigen. Chemotherapy given to them for the lymphoma may reactivate the hepatitis and is potentially fatal. This can be effectively prevented by prophylactic anti-viral therapy, such as lamivudine.11

Treatment

Different types of lymphoma warrant different treatment strategies. Chemotherapy is now the mainstay of therapy for most cases of lymphoma. It may be supplemented by local radiotherapy. For Hodgkin’s lymphoma, the standard ABVD chemotherapy consists of adriamycin, bleomycin, vinblastine and DTIC.

For follicular lymphoma, a small minority of the patients may have clinical localised disease. Involved field radiotherapy is recommended and gives a potential of cure in about half of the patients. For majority of the patients with more advanced follicular lymphoma, the tumour is considered incurable, despite the fact that it often runs a clinically indolent course. Therefore, an initial wait and watch policy is still recommended if the patient is asymptomatic or without any adverse prognostic factors, especially for elderly patients. When treatment is deemed necessary, a variety of chemotherapy regimens have been adopted, from single agent (chlorambucil or cyclophosphamide) to CVP (cyclophosphamide, vincristine and prednisolone) or CHOP (cyclophosphamide, adriamycin, vincristine and prednisolone). Fludarabine as a single agent or in combination with cyclophosphamide (FC) or mitoxantrone and dexamethasone (FND), is also widely
used. The humanised chimeric anti-CD20 monoclonal antibody has been shown to be an effective therapy for CD-20 positive B-cell lymphoma. It is now considered to be a standard to add the monoclonal antibody to chemotherapy. This practice has been shown to improve the duration of remission and survival. A newer form of therapy with radio-labelled anti-CD20 monoclonal antibody has also been shown to be effective in follicular lymphoma.12

For aggressive non-Hodgkin’s lymphomas such as the diffuse large B-cell lymphoma, the CHOP chemotherapy, consisting of cyclophosphamide, Adriamycin, vincristine and prednisolone, is the most widely used. The treatment offers a high potential for cure. Addition of anti-CD20 monoclonal antibody therapy to the regimen also appears to offer additional benefit. There is no evidence that the other more complicated regimens offer an advantage.13 Treatment for lymphoblastic leukaemia simulates that for acute lymphoblastic leukaemia, usually respond poorly to chemotherapy. This practice has been shown to improve the duration of remission and survival. A newer form of therapy with radio-labelled anti-CD20 antibody has been shown to be an effective therapy for CD-20 positive B-cell lymphoma. It is now considered to be a standard to add the monoclonal antibody to chemotherapy. This practice has been shown to improve the duration of remission and survival. A newer form of therapy with radio-labelled anti-CD20 monoclonal antibody has also been shown to be effective in follicular lymphoma.12

High dose chemotherapy with autologous peripheral stem cell rescue is mainly used for treating relapsed diseases. It is most effective when the lymphoma remains chemosensitive. An allogeneic bone marrow transplant may also be indicated in selected patients, for example when the bone marrow is involved and when an HLA identical donor is available.15

With the advances in therapy, the clinical outcome of lymphoma patients has improved significantly. However, the prognosis of some types of lymphoma, such as mantle cell lymphoma and T-cell lymphoma remains poor. Further research on lymphoma is urgently needed. Better understanding of lymphoma may provide effective measures for prevention and even more effective but less toxic therapy.

References

Table 1: WHO Classification for Hodgkin’s Lymphoma
- Classical Hodgkin Lymphoma:
  - Nodular sclerosing
  - Mixed cellularity
  - Lymphocyte rich
  - Lymphocyte depleted (worse prognosis)
- Nodular lymphocyte predominant Hodgkin Lymphoma

Table 2: WHO Classification for B-cell Lymphoma
- B-lymphoblastic lymphoma
- Chronic lymphocytic leukaemia or small Lymphocytic lymphoma
- B-Prolymphocytic Leukemia
- Lymphoplasmacytoid lymphoma
- Splenic marginal Zone lymphoma (Splenic lymphoma with villous lymphocytes)
- Hairy cell leukaemia
- Monoclonal gamopathy of unknown significance / plasmacytoma / myeloma
- Lymphoma of the Mucosa Associated Lymphoid Tissue (MALToma)
- Mantle cell lymphoma
- Follicular lymphoma
- Nodal marginal zone lymphoma
- Diffuse large B-cell lymphoma
- Mediastinal diffuse large B-cell lymphoma
- Intravascular large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt’s lymphoma

Table 3: WHO Classification for T-cell or NK-cell Lymphoma
- T-lymphoblastic lymphoma
- T-prolymphocytic leukaemia
- Large granular lymphocyte leukemia
- Aggressive NK cell leukaemia
- Adult T-cell leukaemia/lymphoma
- Cutaneous T-cell lymphoma
  - Cutaneous anaplastic large cell lymphoma
  - Mycosis fungoides
  - Sezary syndrome
  - Cutaneous anaplastic large cell lymphoma
  - Lymphomatoid papulosis
- Extramedullary NK/T-cell lymphoma
- Enteropathy-type T-cell lymphoma
- Hepatosplenic gamma delta T-cell lymphoma
- Subcutaneous panniculitis like T-cell lymphoma
- Peripheral T-cell lymphoma
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma
- Systemic
- Blastic NK cell lymphoma

Figure 1: Nasal NK/T-cell lymphoma infiltrating the hard