Non-Hodgkin’s lymphoma

CME lecture

Malignant lymphoma is divided into two groups of diseases: Hodgkin’s disease and non-Hodgkin’s lymphoma (NHL), with some contrasting features (Table 1). The condition is not common in the UK: on average, a general practitioner may see one new case every two years. The overall incidence in the UK is about 12 cases per 100,000 per year. About two-thirds of these are of the non-Hodgkin’s type, certain forms of which are now potentially curable. Early diagnosis is thus vital.

The NHLs are a heterogeneous group of malignancies whose behaviour varies from indolent to rapidly lethal; high-grade tumours arise in all age groups, though their incidence increases with age, whilst low-grade tumours are generally confined to later life. They are marginally commoner in men than women and there is a marked geographical variation in incidence. Their incidence is fast increasing (for review see [1]).

Aetiology

Little is known of the aetiology of most types of NHL, but important clues may come from information recently available. First, the human T cell leukaemia-1 virus has an undoubted role in the induction of a particularly aggressive T cell lymphoma seen most often in Japan and the Caribbean (adult T cell leukaemia/lymphoma). Second, the Epstein-Barr virus (a potent stimulus to the immune system and to immortalised cells) has been implicated in some B and T cell lymphomas, the best known being Burkitt’s lymphoma where the virus acts in concert with chronic malaria. Most patients with Burkitt’s lymphoma, which is endemic in young East African populations, have genetic rearrangements of the c-myc oncogene—usually by translocation of this gene on chromosome 8 to the long arm of chromosome 14 where it recombines with the gene coding for immunoglobulin heavy chain. The heavy chain locus is constitutively expressed in B lymphoid cells; thus, translocation of c-myc to this region results in its abnormal expression with resulting deregulation of cell proliferation. In low-grade follicular lymphoma (amongst other B cell neoplasms) there is often a 14:18 translocation [t(14;18)(q32;q21)] in which the BCL-2 gene is simi-

larly affected. Expression of this gene prevents programmed cell death (apoptosis), thus permitting clonal expansion. Thirdly, NHLs associated with immunodepressed states (such as congenital syndromes after organ transplantation) are often bizarre in both presentation and clinical behaviour with a propensity for involvement of the central nervous system. There is strong evidence to suggest viral aetiology in this group. Lastly, at least part of the increasing incidence of high-grade NHL is related to human immunodeficiency virus infection—so much so that it is now an AIDS defining illness. NHLs also occur more frequently in populations exposed to large single doses of radiation, as occurred at Hiroshima and Nagasaki, and are among the most common of the second malignancies seen after previous chemotherapy for cancer.

Despite all this, the cause for most NHLs is still unknown.

Histology

There have been many different classifications of NHL depending on morphological and, more recently, immunophenotypic characteristics. The six best known classifications have been reviewed by an international group, and a working formulation for clinical usage has been devised to harmonise them [2]. In this formulation, lymphomas are grouped into low, intermediate and high-grade malignancy. A further proposal for classification of lymphoid neoplasms, based on all available information, consists of a list of currently recognised clinicopathological entities [3]. In practical terms, however, many oncologists simply refer to low and high-grade as broad management groups (for example, as in the Kiel classification [4], simplified in Table 2).

Most tumours are of the B cell type. Low-grade tumours are either composed of lymphocytes (like chronic lymphocytic leukaemia), lymphoplasmacytoid cells (Waldenström’s macroglobulinaemia) or germinal centre cells (the latter usually grow in a follicular pattern). Low-grade tumours have a relatively indolent clinical course. High-grade tumours are composed of more primitive cells, including those from the proliferating compartment in germinal centres (centroblasts), immunoblasts or lymphoblasts. Their growth pattern is diffuse and they are clinically more malignant in their behaviour. It is in this group, however, that specialist management produces cures.

This article is based on a lecture given during a College CME day, ‘Haematology for general physicians’, on 7 June 1995 by Barry W Hancock MD DCH FRCP, FR CR, Professor of Clinical Oncology, University of Sheffield.
T cell lymphomas account for approximately 10–20% of the tumours and have widely varying histological characteristics. Most common are the peripheral T cell NHLs which have gained the reputation for having a poorer prognosis than their B cell counterparts, with protean clinical presentations. However, factors other than histology are likely to be equally important in determining their prognosis. The indolent skin lymphoma, mycosis fungoides and its variant, the Sézary syndrome (where there are circulating abnormal T lymphocytes (Sézary cells)), are far less common.

Table 1. Contrasting features of Hodgkin's disease and non-Hodgkin's lymphoma.

| Feature                | Hodgkin's disease | Non-Hodgkin's lymphoma |
|-----------------------|-------------------|------------------------|
| Age                   | Younger           | Older                  |
| Male:female ratio     | 3:2               | 6:5                    |
| Presentation          | Neck nodes most common | Unusual nodes or extranodal sites; often generalised |
| Histology             | Rye classification* | High versus low-grade |
| Spread                | Contiguous (unifocal origin) | Generalised (multifocal origin) |
| Treatment             | Localised: radiotherapy | Usually symptomatic for low-grade; intensive chemotherapy for high-grade |
| Others: cyclical chemotherapy +/- radiotherapy | Low-grade: median survival 7–8 years (rarely cured) |
| Progress              | Over two-thirds of patients cured | High-grade: over one-third of patients cured |

* Lukes RJ, Butler JJ. The pathology and nomenclature of Hodgkin's disease. Cancer Res 1996;26:2063–81.

Clinical features

Unexplained persistent lymphadenopathy should always indicate a need for prompt referral for expert assessment and probable biopsy. The presentation of lymphoma is variable but systemic features such as unexplained pyrexia and nocturnal sweating should alert the clinician to this possible diagnosis. Localised lymphadenopathy, particularly in the neck, is a common presentation but there may be more generalised and 'centrifugal' lymphadenopathy, and about 25% start outside the classic lymph node areas—most often the tonsils, gut and skin, but almost any tissue can be affected.

In the differential diagnosis of chronic lymphadenopathy, infection will figure high on the list in younger patients whereas in the older patients secondary carcinoma and lymphocytic leukaemia are the commonest causes of localised and generalised lymphadenopathy, respectively.

Staging

Knowing the stage of the patient’s disease is not so important nowadays for determining treatment but it still has a bearing on prognosis. The Ann Arbor criteria (Table 3) are still useful [5].

In the staging process, full history and examination should be followed by histological examination of an adequate tissue biopsy and relevant investigations, to establish the staging and to define other prognostic markers (Table 4). A full peripheral blood count and film are mandatory because anaemia and raised erythrocyte sedimentation rate are features of more widespread disease. Biochemical investigations should include hepatic and renal function tests, though, of
Table 3. The Ann Arbor staging criteria.

| Stage | Description |
|-------|-------------|
| I     | Single lymph node region involved |
| II    | Two or more lymph node regions involved but on the same side of the diaphragm |
| III   | Involvement of lymph node regions on both sides of the diaphragm |
| IV    | Generalised involvement of one or more extralymphatic organs with or without lymph node disease |

Localised extralymphatic lesions with or without associated lymph node involvement are termed 'E' (extranodal) lesions

| Category | Description |
|----------|-------------|
| A        | Asymptomatic |
| B        | Symptomatic (significant weight loss and/or night sweats and/or unexplained persistent fever) |

Table 4. Unfavourable prognostic features for malignant lymphoma.

| Feature            | Unfavourable prognosis |
|--------------------|------------------------|
| Age                | Older                  |
| Sex                | Male                   |
| Histology type     | Unfavourable features  |
| Stage              | Widespread, bulky disease 'B' symptoms (See Table 3) |
| Performance status | Poor                   |
| Haemoglobin        | Low                    |
| Erythrocyte sedimentation rate | High |
| Serum albumin      | Low                    |
| Serum lactic dehydrogenase | High |
| Response to initial treatment | None |

Table 5. Chemotherapy acronyms (example regimens).

| Acronym       | Description                                      |
|---------------|--------------------------------------------------|
| C(H)OP        | cyclophosphamide, (hydroxydaunorubicin, doxorubicin), Oncovin (vincristine), prednisolone |
| PACE-BOM      | prednisolone, Adriamycin (doxorubicin), cyclophosphamide, etoposide-bleomycin, Oncovin, methotrexate + folinic acid |

should be assessed, since marrow involvement will be found in over 30% of cases; in certain poor prognosis forms, particularly of the lymphoblastic type, cerebrospinal fluid should be cytologically examined.

Treatment

Treatment must be planned on the basis of clinical, histopathological and investigative findings. In general, elderly patients with aggressive lymphomas do less well and experience greater toxicity than younger, fitter patients.

Localised (Stage I, nodal or extranodal) NHL, whatever the histology, is potentially curable by local radical irradiation. In most cases, however, NHL is more widespread. For the low-grade (so-called favourable) type there is no conclusive evidence that intensive treatment of any sort changes the indolent natural history, although complete remissions may be more common in those treated with polychemotherapy and complete remissions more durable than partial remissions. These points remain controversial. Many authorities therefore pursue an expectant policy, instituting treatment only when the patient's lymphadenopathy becomes symptomatic, systemic symptoms develop or a vital organ is involved. Such treatments (which are palliative only) may involve local low-dose irradiation, combination chemotherapy (COP) (see Table 5 for drug regimens) or, more commonly, single agent oral chemotherapy with, for example, chlorambucil. In high-grade NHL (other than those with truly localised tumour) intensive intravenous chemotherapy is mandatory, assuming that the patient's general condition allows it. Multiple agents are administered in many different regimens but most commonly either in pulses every three to four weeks over a period of six months (for example, CHOP) or weekly for 12 weeks (for example, PACE-BOM). In certain less common types of high-grade disease (particularly lymphoblastic in young patients) acute lymphoblastic leukaemia-type regimens are often used.

One promising area is the role of very high-dose chemotherapy with autologous bone marrow or peripheral blood stem cell transplant. In high-grade NHL if there is no response to first-line conventional chemotherapy, it is unlikely that any salvage treatment will help; the role of autograft as an integral part of course, extensive involvement of liver and kidneys can occur before such tests become abnormal. Enzyme activity in the blood, such as alkaline phosphatase, and particularly lactic dehydrogenase, may be elevated as a marker of poor prognosis. Radiological investigations must include chest x-ray to detect mediastinal and hilar lymphadenopathy and some investigation to establish the presence of abdominal disease. In the past, this was often lymphangiography; current 'state of the art' computed tomography scanning has made this redundant, particularly as it is now evident that unless the lymphoma is truly localised, chemotherapy is likely to be needed as part of the planned treatment. In low-grade NHL, abdominal ultrasound is probably sufficient for most clinical practice.

Clinical staging tends to underestimate the incidence of systemic disease. Bone marrow trephines
first-line treatment protocols is therefore being evaluated. In low-grade lymphoma the place for high-dose chemotherapy with autograft is even less clear; the transplanted bone marrow (or stem cells) is often ‘purged’ using appropriate monoclonal antibodies to reduce the risk of reinfusing lymphoma cells after ablative therapy.

In low-grade NHL, several new antimetabolite cytotoxic drugs are under trial, including the chemically related purine analogues fludarabine and 2-chlorodeoxyadenosine. Also, interferon-α, with and after chemotherapy, prolongs remission and may prolong survival.

**Side-effects**

The patient with lymphoma will suffer to a greater or lesser degree any of the acute and chronic effects of radio- and chemotherapy (Table 6). Quality of life has been improved by the selective use of new anti-emetics (the 5HT3 antagonists) and by improved supportive care. A particular problem with lymphoma is the possibility of a tumour lysis syndrome; a rapid rise in uric acid can give rise to renal failure if the patient is not pretreated with allopurinol, and gross electrolyte disturbances, particularly hyperkalaemia, should be anticipated. The most serious problem, however, is infection: lymphoma involves tissues of the immune system, and immunosuppression may be severe, compounding the myelosuppression seen with intensive chemotherapy. Neutropenic sepsis, which may be fatal if expert diagnosis and treatment are delayed, mandates early referral to the treatment centre for appropriate intravenous antibiotic therapy. However, one promising development in this field is the use, when appropriate, of haemopoietic growth factors to accelerate bone marrow recovery.

Many of the chemotherapy regimens used in lymphoma contain alkylating agents; therefore, in the long term infertility is a problem (particularly in men so that pre-treatment sperm cryopreservation may be needed), and there is a greater risk of second malignancy.

**Prognosis**

The prognosis varies enormously with histology and stage; for truly localised high-grade NHL, survival rates of 60–80% disease-free at five years are the rule; for widespread disease treated with chemotherapy the rates are about 30–40%. With low-grade NHL however, the outlook has not improved: the median survival is 7–8 years. Eventually the disease becomes clinically and often histologically more aggressive; even intensive chemotherapy at this stage rarely gives prolonged responses.

**Conclusions**

The undoubted benefits of modern treatment for lymphoma should not lead to complacency. It may well be that high-grade NHL is now potentially curable, but patients are still dying of this disorder and there are long-term complications of treatment. For low-grade NHL the outlook has not improved over the past two or three decades. New approaches must still be explored in large cohort and multicentre randomised studies with long-term follow-up involving specialist oncology centres.

**References**

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