Classic diseases revisited

Management of non-Hodgkin's lymphomas

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Summary

The non-Hodgkin's lymphomas (NHL) are a heterogeneous group of disorders characterised by malignant proliferation of lymphoid cells. The cellular origin is relatively well established with subtypes corresponding to the various stages of lymphocyte differentiation. The term encompasses a hotchpotch of conditions with very different morphological appearance, behaviour and clinical outcome. NHL comprise 2.4% of all cancers, with incidence increasing with age. The commonest presentation is with progressive lymphadenopathy, though extranodal manifestations are present in a significant proportion. The clinical behaviour ranges from a benign, indolent course to rapidly progressive disease; prognosis varies from weeks to many years. Treatment is correspondingly diverse, from 'watchful waiting' to high-dose chemotherapy with bone marrow stem cell transplantation. Cure is possible in an increasing number of patients and much interest currently lies in identifying patients with high-risk disease necessitating the use of intensive treatment regimens.

Keywords: non-Hodgkin's lymphoma

Aetiology

Non-Hodgkin's lymphomas (NHL) arise from a single mutant lymphoid cell giving rise to a malignant clone. The genetic changes associated with lymphomatous transformation have been extensively investigated and have contributed greatly to knowledge of tumourigenesis in general. Chromosomal abnormalities can be identified in more than 85% of NHL specimens.^{1 2} Certain conditions are known to predispose to the development of NHL (box 1). Viral infection has been linked with particular subtypes, eg, Epstein-Barr virus and endemic Burkitt's lymphoma, HTLV-1 and adult T-cell leukaemia/lymphoma, but there is no convincing evidence to link viral aetiology with most NHL.

Epidemiology

True incidence rates for NHL are difficult to calculate due to the heterogeneous nature of the condition. The incidence in the UK for all types is at least 8/100 000, and this has been rising in recent years. HIV-associated NHL and the increased use of immunosuppressive therapy partly explain this rise but are by no means the whole story. The incidence of NHL increases with age. There is a marked worldwide geographical variation, particularly striking with the distribution of endemic Burkitt's lymphoma and adult T-cell leukaemia/lymphoma. The majority of NHLs are of B-cell origin, though it is important to identify those of T-cell phenotype as the natural course and treatment can be very different.

Clinical presentation

The usual clinical presentation is with lymphadenopathy or an extranodal mass. Systemic 'B' symptoms of fever, night sweats or weight loss are present in up to one third of patients at diagnosis.

Classification

The histopathological classification of NHL has provoked frustration and controversy for pathologists and clinicians alike. Numerous classification systems have been proposed over the past 30 years with none gaining universal acceptance. Initial classifications were based on morphological appearance alone but modern immunological and molecular techniques have enabled more precise classification according to putative cell of origin. The ideal classification should be reproducible and identify specific disease entities with prognostic significance, thereby permitting rational treatment planning. In practice, no system is perfect and all include a large number of unclassifiable cases.

Most histopathologists in the UK and Europe have used the Kiel classification,³ whereas the National Cancer Institute Working Formulation⁴ has held sway in the US. This has made the comparison of clinical trial results very difficult. The need for international terminological consensus has long been recognised. In 1990, the International Lymphoma Study Group was founded with the intention of achieving this goal. A pragmatic approach was employed, and a list of disease entities was produced, based on morphology, immunophenotype, molecular genetics and clinical behaviour. Contentious subtypes were included as provisional entities and the possibility of unclassifiable cases was allowed for. No attempt was made to identify tumour grade, a point of concern for many clinicians. The results were published in 1994 as the *Revised European-American Lymphoma Classification* (REAL, box 2)⁵ and have been widely disseminated. Many criticisms have been levelled at this paper, but it is important to remember that it was published as a proposal requiring validation and subsequent modification. An internationally accepted and employed classification system will be a major advance in lymphoma management.

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Conditions predisposing to development of NHL

Congenital

- ataxia telangiectasia
- Wiskott-Aldrich syndrome
- common variable immunodeficiency
- severe combined immunodeficiency
- X-linked lymphoproliferative syndrome
- coeliac disease

Acquired

- organ transplants
- immunosuppressive therapy
- HIV infection
- HTLV-1 infection
- *H pylori* gastritis
- Hashimoto's thyroiditis
- Sjögren's syndrome
- Hodgkin's disease

Box 1

Ann Arbor staging classification

Stage	Definition
I	Involvement of a single lymph node region (I) or a single extranodal organ or site (I _e)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localised involvement of an extranodal organ or site in addition (II _e)
III	Involvement of lymph node regions on both sides of the diaphragm (III); may include involvement of the spleen (III _s) or localised extranodal disease (III _e)
IV	Disseminated involvement of one or more extranodal sites, eg, liver, bone marrow, lung, skin (with or without associated lymph node involvement)

The suffixes A or B denote the absence or presence of fever, night sweats or weight loss of >10% body weight in the preceding 6 months.

Box 3

Investigation of NHL

- physical examination
- histological diagnosis
- full blood count
- erythrocyte sedimentation rate
- urea and electrolytes
- liver function tests
- lactate dehydrogenase
- β₂-microglobulin
- serum immunoglobulins
- chest X-ray
- CT scan of chest and abdomen
- bone marrow aspirate and trephine

Box 4

Revised European-American classification of lymphoid neoplasms

B-cell neoplasms

- I Precursor B-cell neoplasm: precursor B-lymphoblastic leukaemia/lymphoma
- II Peripheral B-cell neoplasms
 - 1 B-cell chronic lymphocytic leukaemia/prolymphocytic leukaemia/small lymphocytic lymphoma
 - 2 Lymphoplasmacytoid lymphoma/immunocytoma
 - 3 Mantle cell lymphoma
 - 4 Follicle centre lymphoma, follicular: provisional cytologic grades I (small cell), II (mixed small cell and large cell), and III (large cell); provisional subtype: diffuse, predominantly small cell type
 - 5 Marginal zone B-cell lymphoma: extranodal (MALT-type ± monocytoid B cells); provisional subtype: nodal (± monocytoid B cells)
 - 6 Provisional entity: splenic marginal zone lymphoma (± villous lymphocytes)
 - 7 Hairy cell leukaemia
 - 8 Plasmacytoma/plasma cell myeloma
 - 9 Diffuse large B-cell lymphoma. Subtype: primary mediastinal (thymic) B-cell lymphoma
 - 10 Burkitt's lymphoma
 - 11 Provisional entity: high grade B-cell lymphoma, Burkitt-like

T-cell and putative NK-cell neoplasms

- I Precursor T-cell neoplasm: precursor T-lymphoblastic lymphoma/leukaemia
- II Peripheral T-cell and NK-cell neoplasms
 - 1 T-cell chronic lymphocytic leukaemia/prolymphocytic leukaemia
 - 2 Large granular lymphocyte leukaemia: T-cell type, NK-cell type
 - 3 Mycosis fungoides/Sézary syndrome
 - 4 Peripheral T-cell lymphomas, unspecified. Provisional cytologic categories: medium-sized cell, mixed medium and large cell, large cell, lympho-epithelioid cell; provisional subtype: hepatosplenic γδ T-cell lymphoma; provisional subtype: subcutaneous panniculitic T-cell lymphoma
 - 5 Angio-immunoblastic T-cell lymphoma
 - 6 Angiocentric lymphoma
 - 7 Intestinal T-cell lymphoma (± enteropathy associated)
 - 8 Adult T-cell lymphoma/leukaemia
 - 9 Anaplastic large cell lymphoma, CD30⁺, T- and null-cell types
 - 10 Provisional entity: anaplastic large cell lymphoma, Hodgkin's-like

Box 2

Staging

The staging of NHL is based on the Ann Arbor system originally developed for Hodgkin's disease (box 3).⁶ This system is less accurate in identifying prognostic subgroups in NHL due to the pattern of disease spread. NHL is much more likely than Hodgkin's to be widespread at diagnosis. Recommended staging investigations are indicated in box 4.

Prognostic factors

The purpose of staging patients with NHL is to identify prognostic subgroups. It is apparent that the Ann Arbor classification alone does not do this consistently. Other clinical variables have been employed to generate a system for stratifying patients into risk groups. This has important implications for treatment planning. Patients identified as high risk may not be effectively treated by current regimens and experimental therapy may be justified. Conversely, patients at low risk may be effectively treated with current approaches and can be spared the additional toxicity and complications of more intensive regimens (table). One such validated scheme exists for aggressive NHL. The International Index⁷ was based on the analysis of presenting features and outcome in 2031 patients. Four risk groups were identified using a scoring system based on age, Ann Arbor stage, serum lactate dehydrogenase levels, performance status and number of extranodal sites involved. The predicted 5-year survivals of the groups were 73%, 51%, 43%, and 26%. The value of such an index lies in the ability to predict outcome and guide treatment planning.

The International Index has been applied to low-grade lymphoma but it does not seem to have the same discriminatory power in this situation. Several stud-

Table Potential complications of therapy

Stage	Chemotherapy	Radiotherapy
Acute	myelosuppression nausea & vomiting alopecia	local skin reaction mucositis loss of taste myelosuppression alopecia
Late	infertility second malignancy	hypothyroidism pulmonary fibrosis cardiomyopathy

ies have attempted to establish prognostic parameters in indolent NHL,⁸⁻⁹ but none has gained widespread acceptance.

Management of NHL

GENERAL PRINCIPLES
Most patients will receive chemotherapy and/or radiotherapy, though the diagnosis of lymphoma does not necessarily indicate the need for cytotoxic therapy. This is particularly the case in low-grade NHL where early treatment has not improved overall survival. Surgery alone may rarely be curative and the recently recognised entity of *Helicobacter pylori*-associated gastric MALToma may be successfully treated with antibiotics alone. Quality of life should be prominent in treatment planning, with consideration of the individual's general health, histological subtype, extent of disease and measurable prognostic factors. Currently greater than 50% of new cases of NHL occur in patients over 60 years¹⁰ in whom coexisting chronic disease may limit treatment. Elderly patients also appear to have a more aggressive disease.¹¹

INDOLENT NHL
Most of the available data pertain to follicular lymphoma,¹² which is the commonest type of NHL in the West. The usual presentation is with localised lymphadenopathy, though the majority of patients (80–85%) have widespread disease at diagnosis. The median survival is 4–10 years,⁸⁻¹³⁻¹⁵ with cure only rarely achieved. Transformation to a more aggressive tumour occurs in up to 10% of cases with subsequent poor outlook.
Localised follicular lymphoma (stage 1) presents the best opportunity for cure, and this may be achieved by radiotherapy. The relapse rate is 50%, most occurring within 5 years. Risk of relapse is associated with tumour bulk, age and presence of B symptoms. Adjuvant chemotherapy does not improve overall survival but does improve relapse-free survival.

The aim of treatment in most cases of disseminated follicular NHL is symptom control rather than cure. Horning and Rosenberg¹⁶ showed that treatment abstinence until disease progression did not alter survival compared to those treated immediately after diagnosis. Such 'watchful waiting' may be proposed for patients in the absence of disease-related symptoms or adverse prognostic factors.

Single agent chemotherapy with an alkylating agent such as chlorambucil or cyclophosphamide has been the standard treatment for follicular lymphoma. Response rates are of the order of 70–80%, though more than 70% relapse within 5 years. First-line therapy may then be repeated but responses tend to become shorter in duration until the disease becomes unresponsive. Combination chemotherapy such as 'CVP' (cyclophosphamide, vincristine and prednisolone) or 'CHOP' (cyclophosphamide, adriamycin, vincristine and prednisolone) has not been shown to affect overall survival.¹⁷⁻¹⁸

The purine analogues fludarabine and 2-chlorodeoxyadenosine have been studied in indolent NHL.¹⁹⁻²² Response rates have been between 50 and 80% but no convincing improvement in overall survival has been shown. The additional toxicity and cost of these agents should also be considered. Alpha-interferon (α IFN) is active in low-grade NHL when used alone. However, it has predominantly been used either concomitantly with conventional chemotherapy during induction²³⁻²⁴ or as maintenance therapy after maximal response to first-line treatment.²⁵⁻²⁶ The optimal timing, dose or duration of α IFN therapy has yet to be established.

Intensive treatment regimens have been studied in an attempt to reduce the high relapse rate, particularly in younger patients. The role of myeloablative chemoradiotherapy with autologous bone marrow stem cell transplant is under evaluation in this small group of highly selected patients.

HISTOLOGICALLY AGGRESSIVE NHL
The early mortality of aggressive NHL is high but patients who do go into remission may have prolonged disease-free survival and up to one third may be cured. This contrasts with the situation in indolent NHL. Risk-adapted strategies are used according to accurate staging and assessment of prognostic factors.

In localised disease, radiotherapy gives good complete remission rates but is associated with a high relapse rate. There is a consensus that combination chemotherapy followed by involved field radiotherapy is the optimum treatment for these patients.

Stage II to IV disease requires combination chemotherapy. The standard regimen is CHOP, which was introduced over 20 years ago. No subsequently intro-

duced regimen has shown a convincing advantage over CHOP. Presently 50–60% of patients will obtain a complete remission, although only half of these will be cured. Radiotherapy is usually given to areas of disease bulk following chemotherapy.

TREATMENT OF RELAPSE

Relapse following initial therapy confers a poor outlook with long-term survival less than 10%. Salvage treatment may include further chemotherapy with or without radiotherapy, or high dose ablative chemotherapy with autologous bone marrow rescue. It is apparent that this strategy is only effective in those patients showing chemosensitivity to conventional treatment.^{27 28}

Autologous bone marrow transplantation has also been considered as primary treatment in patients with poor prognostic factors. Such early treatment intensification requires further validation before it is accepted as standard practice. Allogeneic bone marrow transplantation has been performed in a small number of poor prognosis patients with resistant disease. Age-related toxicity and procedural mortality is high (>20%) with availability restricted due to the need for a matched donor.

Mantle cell lymphoma

Mantle cell lymphoma has been identified as a specific disease entity in the last 5 years²⁹ and merits particular mention. Regarded as a low-grade tumour in previous classifications, it has a median survival of only 36 months and is incurable by current treatment approaches. Widespread disease is usually present at diagnosis involving lymph nodes, spleen, bone marrow and extranodal sites such as the gastrointestinal tract. Initial response rates to treatment are high but the majority of patients relapse within 2 years. There is some evidence that high dose myeloablative chemotherapy and total body irradiation followed by stem cell rescue in first remission may give long-term disease-free survival.³⁰

Extranodal disease

Up to 40% of cases of NHL arise in extranodal sites.³¹ Any organ can be involved and the disease can present to virtually any medical specialist. For this reason accurate incidence figures are difficult to obtain. Many of the histological categories of the conventional classifications are irrelevant to extranodal NHLs but some attempt has been made in the recent REAL proposals to rectify this situation. By virtue of the number of medical specialists involved, treatment guidelines have been almost non-existent. This situation is now changing as multidisciplinary groups are being established, eg, in skin lymphomas, to work together and establish 'best practice' in these uncommon disorders and, most importantly, to record outcome.

By far the most common extranodal lymphomas are those which involve the gut. Gut lymphoma is a difficult area with much debate and controversy over classification, staging and treatment. Most published series are small, non-randomised and lack uniformity, thus precluding proper comparison. Treatment can include surgical resection, chemotherapy, radiotherapy or a combination but optimal management has yet to be defined.

MALTomas (marginal zone lymphomas) arise in the mucosa-associated lymphoid tissue (MALT). MALT is found in the normal gut as Peyer's patches, which initiate immune responses in the presence of antigen. MALT may also be acquired in areas normally devoid of lymphoid tissue. This appears to occur in response to inflammatory processes such as infection, as in *H pylori* gastritis, or autoimmune processes such as Hashimoto's thyroiditis or Sjögren's syndrome. It is believed that a malignant clone can replace the normal reactive lymphoid population out of which lymphoma may develop. It has been demonstrated that MALT appears in the stomach in response to infection by *H pylori*³² and that the organism is present in over 90% of gastric MALT lymphomas.³³ This suggests that the lymphoma is antigen driven and eradicating the infection might inhibit the tumour. There is evidence that anti-*H pylori* treatment with antibiotics causes regression of gastric MALToma.³⁴ Interestingly, regression may not occur immediately after treatment and may take anywhere between three and 18 months.³⁵

T-Cell lymphomas

Lymphomas of T-cell origin exhibit great morphological diversity with subtypes still being delineated. Lymphoblastic lymphoma is a high-grade tumour akin to acute lymphoblastic leukaemia, requiring intensive treatment regimens. Periph-

eral T-cell lymphomas arise from mature, post-thymic T cells and comprise 10–15% of all NHL. The prognosis of peripheral T-cell lymphoma is generally worse than that of B-cell NHL with conventional therapy.^{36–37} Anaplastic large cell lymphoma may respond to CHOP chemotherapy with similar outcome to diffuse large cell B-NHL.³⁸ Other peripheral T-cell NHL respond less reliably, with optimal treatment yet to be defined.

Conclusion

Non-Hodgkin's lymphoma is an umbrella term to describe a family of conditions with diverse clinical features at presentation. Many patients are now cured of their disease but mortality remains significant. Improved survival in the future could be effected by new treatment approaches or by more effective targeting of current therapies using improved classification systems and risk stratification.

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