Non-Hodgkin's lymphoma

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Epidemiology

Non-Hodgkin's lymphoma (NHL) is the seventh commonest malignancy in the UK, with a reported incidence of 14.8 and 9.7 per 100,000 in men and women, respectively (Cancer Research Campaign, 1996 figures). The incidence is increasing across the western world at an annual rate of 3–4%[1]. There have been improvements in diagnostic techniques, including the more widespread application of molecular testing, which may have increased the sensitivity of detection. There are also increasing numbers of immunosuppressed individuals as a result of HIV infection, and also because of organ transplantation which predisposes to NHL. However, these factors, together with an increasingly ageing population, fail fully to explain the consistent increase in incidence across all adult age groups.

Classification

The lymphomas represent a heterogeneous group of malignant disorders with widely varying biological and clinical features. Their classification has repeatedly changed, leading to some confusion. The current system used in the UK is the Revised European American Lymphoma (REAL) classification[2]. This recognises NHL as a number of distinct disease entities and moves away from the concept of high, intermediate and low grade diseases. These terms are broadly applicable at a clinical level, but can be misleading. An example of this is mantle cell lymphoma, a subgroup of NHL comprising about 5% of all diagnoses. This is a 'low grade' lymphoma, yet it is resistant to treatment and shows a continuing pattern of relapse even following aggressive treatment modalities. With treatment, there is a five-year survival of approximately 25%, which is considerably worse than the majority of 'high grade' diseases.

Prognostic factors

In addition to the REAL classification, a robust prognostic scoring system has been developed[3]. It has long been appreciated that within the same lymphoma subtype there are factors which help predict patients with a poor outcome, for example the presence of 'B' symptoms (weight loss, night sweats and fevers). The International Prognostic Index (IPI) divides patients into four specific risk groups at diagnosis: high, high-intermediate, low-intermediate and low.

The factors which make up the index (Table 1) are:

- age
- performance status
- stage of disease
- number of extranodal sites of disease
- serum lactate dehydrogenase.

The IPI was originally developed from data on aggressive lymphomas, but has proved applicable to all lymphoma subtypes. The five-year survival rates for patients with aggressive NHL by IPI are shown in Table 2 and Fig 1[4].

Until recently, clinical studies were not stratified by IPI, and this wide discrepancy in outcome may have confounded trial results. For example, the trials of high dose chemotherapy (HDT) with a stem cell transplant as initial treatment for aggressive NHL have consistently failed to demonstrate any survival benefit. However, when retrospective analysis removes those patients who were expected to do well with conventional therapy, there is an advantage for poor risk patients receiving HDT. Many current studies utilise REAL and are now IPI stratified.

Diagnosis

The majority of patients present with painless lymphadenopathy. Although infections and inflammatory conditions can lead to lymphadenopathy, persistently enlarged nodes require surgical excision. Fine needle aspiration is not adequate if lymphoma is suspected, for several reasons:

- Tumour cells do not always uniformly invade lymph nodes, so normal cytology does not exclude disease.
- Reactive and malignant lymphocytes can be morphologically similar.
- It is increasingly important to subclassify NHL, for which fresh intact nodal tissue is ideal.
- Lymphomas may present in many other ways to the general physician, with an increasing number presenting in extranodal sites such as the gastrointestinal tract.

Table 1. Factors independently prognostic of overall survival in non-Hodgkin's lymphoma: (a) score; (b) risk group.

(a)	Score	0	1
	Age (years)	≤60	>60
	Performance status	0 or 1	2, 3 or 4
	Stage	I or II	III or IV
	Extranodal involvement	<2 sites	≥2 sites
	Lactate dehydrogenase	Normal	High

(b)	Risk group	No. of risk factors
	Low	0 or 1
	Low-intermediate	2
	High-intermediate	3
	High	4 or 5

Constitutional symptoms (fevers, weight loss or drenching night sweats) are associated with NHL but are common in many other conditions. In general, patients with NHL and B symptoms have a significant tumour load which usually makes diagnosis straightforward. If clinical examination fails to reveal obvious lymphadenopathy, computed tomography scanning should detect nodal masses. In this setting, a bone marrow examination is rarely helpful. In a patient with constitutional symptoms, a normal blood count and no radiological or clinical evidence for NHL, the marrow is almost invariably normal and a different diagnosis should be considered.

Many lymphoma subtypes are associated with specific cytogenetic abnormalities. For example:

- (14;18) in follicular NHL
- (8;14) in Burkitt's NHL
- (11;14) in mantle cell NHL.

With increasing application of molecular testing, particularly polymerase chain reaction, and more recently fluorescence *in situ* hybridisation, it has become relatively easy to detect these translocations. This can be helpful to differentiate between reactive and malignant lymph nodes where the histology is inconclusive, but it can also be applied following therapy to detect evidence of minimal residual disease. The newly evolving technique of microarray analysis, with which multiple known translocations can be looked for simultaneously, may in future not only be used for NHL diagnosis but may lead to reclassification based on molecular abnormalities rather than on histological features.

Treatment

Initial treatment has changed little over the last three decades for the majority of patients with NHL. Where disease is localised, radiotherapy is often employed irrespective of disease type. For aggressive lymphomas, the drug combination cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) remains the gold standard. A number of five- and six-agent regimens briefly appeared superior, but this was not confirmed in large phase III studies[5]. Following relapse, salvage HDT, consolidated by an autologous transplant, is evidence-based standard therapy[6], but applicable only to younger patients.

Treatment in indolent lymphoma is effectively palliative but, with median survivals of ten years in the commonest subtypes, the fact that the disease is not 'curable' may be irrelevant. Many drugs will induce remissions for these lymphomas. Increasingly, purine analogue drugs, particularly fludarabine, are being used in the indolent lymphomas, usually in the relapsed setting and often in combination with other chemotherapeutic agents. Purine analogues lead to a profound lymphocytopenia, which can last for many months post-therapy and predisposes these patients to opportunistic infections, thus making *Pneumocystis carinii* pneumonia prophylaxis essential.

Table 2. Outcome according to risk group defined by the International Prognostic Index for aggressive non-Hodgkin's lymphoma.

Risk group	Survival rate (%) (5-year)
Low	73
Low-intermediate	51
High-intermediate	43
High	26

New approaches

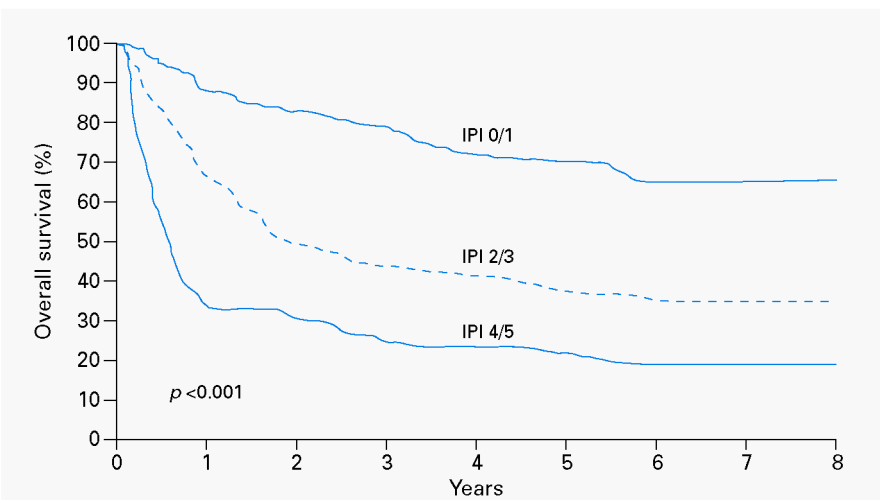
Two potential advances in the management of NHL are becoming established in clinical practice.

Monoclonal antibody therapy

Lymphoma provides a good target for monoclonal antibody therapy as the malignant cells have abundant membrane-bound antigens confined to the tumour and renewable tissue. Antibodies against CD20, a membrane-bound antigen found on many forms of B cell lymphoma, have been developed and are now licensed. This antibody binds to the cell surface and kills tumour cells through a number of mechanisms including cell-mediated and complement-mediated cytotoxicity and the induction of apoptosis.

Treatment is given by weekly infusion, and is generally well tolerated although immediate hypersensitivity reactions can occur. However, it does not have the side effects commonly associated with chemotherapy, namely hair loss, nausea, vomiting and suppression of the bone marrow. Response rates of up to 60% have been seen in follicular lymphomas[7]

Fig 1. The five-year overall survival rates for patients with aggressive non-Hodgkin's lymphoma, illustrating the impact of prognostic factors (IPI = International Prognostic Index) (from Ref 4, with permission).



when used as a single agent, but the exciting prospect is its combination with standard chemotherapy where response rates appear significantly better than with chemotherapy alone[8]. In newer agents the anti-CD20 antibody is conjugated with a radioactive moiety which effectively delivers local radiotherapy directly into the tumour, often with impressive clinical results[9].

Bone marrow (stem cell) transplantation

The other evolving field is bone marrow (stem cell) transplantation. Autologous transplantation is established in the management of relapsed aggressive NHL, and also in selected younger patients with more indolent diseases. Unfortunately, the relapse rate remains high with this approach. Use of allogeneic stem cells from a compatible donor leads to an immune-mediated graft versus lymphoma effect which can eliminate residual disease. This markedly reduces the relapse rate, but has not translated into longer survival because of significant transplant related mortality. A major advance has been the development of reduced intensity 'mini transplants' in which non-myeloablative conditioning is employed. Although doses are less than with a conventional transplant, sufficient immunosuppression is delivered to ensure donor marrow engraftment which repopulates the marrow as a consequence of an immune-mediated graft versus host reaction. This therefore moves away from the concept that it is necessary to create space for the incoming marrow to engraft by giving large doses of conditioning treatment. As a consequence, transplant related mortality has fallen and allogeneic transplantation is being increasingly explored, particularly in more elderly and frail patients. It remains to be seen if mini transplantation will become part of routine practice.

Conclusion

As with all forms of cancer, it is important for patients with NHL to be referred to the appropriate local clinic. Patients should be offered a multidisciplinary approach to both diagnosis and therapy. The latter may require a combination of treatments including chemotherapy, radiotherapy, transplantation and, in future, immune-based therapies. This needs to be tailored to the specific subtype of disease and, where possible, patients should be enrolled in large studies to improve outcome further.

Key Points

- **Non-Hodgkin's lymphomas (NHL) represent a heterogeneous group of malignant disorders with widely varying biological and clinical features**
- **The Revised European American Lymphoma (REAL) classification recognises specific disease entities**
- **There is an unexplained increase in incidence of NHL across the western world**
- **The International Prognostic Index (IPI) divides patients into four specific risk groups**
- **Management should be within a specialist clinic employing a multidisciplinary approach**

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