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Regular Review

Modern management of non-Hodgkin's lymphoma

G M MEAD, J M A WHITEHOUSE

The non-Hodgkin's lymphomas are among the most diverse and challenging diseases treated by physicians. A mass of clinical data has now accumulated from prospective studies begun in the 1970s. In addition, recent advances in our understanding of the pathogenesis of these diseases have provided new insights and may in the future provide opportunities for new approaches to treatment.

Though the incidence rates of non-Hodgkin's lymphoma are low—3746 new cases in Britain in 1982, representing 2% of malignant tumours (excluding skin cancers)—the curability of certain subtypes and the clinical course of others increase the importance of these diseases. These tumours may occur at almost any site and will therefore be encountered by clinicians in all specialties. They are commonly highly sensitive to irradiation and to a wide variety of drugs used alone or in combination. The correct choice and timing of treatment are crucial, however, if optimal results are to be obtained, and early referral to a specialist is recommended.

Pathogenesis

The non-Hodgkin's lymphomas are monoclonal proliferations of B cells, T cells, or histiocytes.

The B cell tumours are the most frequent and have been most intensively studied because the neoplastic cells have on their surface or in their cytoplasm a monoclonal immunoglobulin molecule which provides an effective marker. Antibodies to the heavy and light chains of this immunoglobulin molecule have proved useful in distinguishing B cell lymphomas from other tumours by identifying monotypic tumour populations.¹ Extension of the tumour to the peripheral blood² or bone marrow may also be detected with these methods. Antibodies raised to idiotypic tumour determinants (antigens specific to the individual tumour) have shown unrecognised (and possibly physiological) alterations in the phenotype with time³ and biconality in some cases.⁴ These antibodies have also been used therapeutically.^{5,6} More recently the study of the rearrangement of immunoglobulin genes in tumour cell deoxyribonucleic acid (DNA) has been used to identify B cells and more specifically to detect monoclonal B cell proliferation.⁷

T cells may be labelled with a battery of monoclonal

antibodies, although these cannot be used reliably to identify monoclonal proliferations as is possible with the B cell lymphomas. Immunohistochemical identification of T cell lymphomas is further complicated by the large number of reactive T cells often found in B cell lymphomas. Confirmation of the T cell phenotype and monoclonality is now possible, however, by identifying the rearrangement of T cell receptor genes in tumour cell DNA.⁸

The true histiocytic lymphomas are rare and have not been well evaluated with monoclonal antibodies.

Histopathology

The classification of non-Hodgkin's lymphomas has proved a major source of contention. For at least a decade the Rappaport classification was the most widely used.⁹ More recently, and prompted by increasing knowledge, new classifications have been evolved; at least six are in international use.¹⁰ Most rely on morphological features alone, but two (Kiel¹¹ and Lukes and Collins¹²) incorporate knowledge about T and B cell lineage and maturation. Whichever classification is used intra- and inter-pathologist reproducibility has proved poor in reporting subtypes.¹³ The United States National Cancer Institute studied all the classifications and found that none provided more meaningful clinical data than any other. The pathologists cooperating in this study then devised a "working formulation" (table), intended to act as a link between classifications.¹⁰ Unfortunately this takes no account of immunological data, but none the less it has proved invaluable to clinicians as it is linked to a large clinical database and is widely used in modern clinical series. For these reasons the working formulation will be used in the remainder of this article.

Non-Hodgkin's lymphomas are pathologically complex. Composite lymphomas¹⁴ (two subtypes occurring at a single site) and discordant lymphomas¹⁵ (two subtypes present at anatomically separate sites) occur in 10-15% of cases and were first recognised when multiple biopsy specimens were obtained at staging laparotomy. Histological evolution of the disease—from low grade to intermediate or high grade disease—occurs commonly on follow up and is clinically important.¹⁶ Repeated biopsies in patients with relapsing

*National Cancer Institute working formulation for non-Hodgkin's lymphomas***Low grade**

- A Malignant lymphoma, small lymphocytic (SL)
- B Malignant lymphoma, follicular. Predominantly small cleaved cell (FSC)
- C Malignant lymphoma, follicular. Mixed small cleaved and large cell (FM)

Intermediate grade

- D Malignant lymphoma, follicular. Predominantly large cell (FLC)
- E Malignant lymphoma, diffuse. Small cleaved cell (DSC)
- F Malignant lymphoma, diffuse. Mixed small and large cell (DM)
- G Malignant lymphoma, diffuse. Large cell (DLC)

High grade

- H Malignant lymphoma. Large cell, immunoblastic
- I Malignant lymphoma. Lymphoblastic (LL)
- J Malignant lymphoma. Small non-cleaved (including Burkitt's lymphoma)

Miscellaneous

Composite	Extramedullary plasmacytoma
Mycosis fungoides	Unclassifiable
Histiocytic	Other

disease or disease behaving atypically are, therefore, an essential component of the management of these patients. Expert review by a pathologist with extensive experience of this disease and access to immunodiagnostic techniques is essential before treatment.

Staging

Rational planning of treatment for patients with non-Hodgkin's lymphoma requires accurate staging. All patients should undergo routine haematological and biochemical testing, supplemented by a chest x ray film, abdominal computed tomography, and abdominal ultrasound examination. Lymphangiography remains the most sensitive technique for assessing whether the para-aortic and iliac nodes are affected; it is best used when no abdominal mass is palpable. Unilateral bone marrow trephine and aspiration samples should also be obtained from the posterior iliac crest. Investigations with positive results will need to be repeated sequentially during treatment to ensure a return to normality. Other investigations (bone scanning, barium studies, and so on) may be needed if there is evidence of tumour at other sites. Staging laparotomy is not indicated for these patients, many of whom are elderly, since it rarely influences treatment policies.¹⁷

Treatment is determined on the basis of the histological findings, the bulk and site of the disease, and the patient's age and medical history.

Low grade lymphoma

This group (comprising 40% of cases) includes follicular small cleaved and follicular mixed lymphoma—both of B cell lineage—and small lymphocytic lymphoma—commonly of B cell, but occasionally of T cell lineage.¹⁰

These diseases often have a long clinical course and usually present in patients of middle to late age with enlarged lymph

nodes, which commonly wax and wane in size (spontaneous regression is well known in these tumours). Primary presentation at extranodal sites is uncommon. After staging 10-15% of patients are in stage I and II and the remainder in stage III or IV. Bone marrow infiltration is common¹⁰; staging laparotomy is not indicated.

Patients with stage I and probably those with stage II disease should be treated with radiotherapy.¹⁸ Many will remain free of relapse for several years, but the term "cure" is inappropriate until the follow up has extended for at least 10-15 years since late relapse may occur. The extent of irradiation necessary for "cure" is unknown; it is our practice to treat only fields in which there is disease, but many centres in the United States use wide field treatment. Adjuvant chemotherapy is not indicated.¹⁹

Patients with more advanced follicular small cleaved or small lymphocytic lymphoma are not curable with chemotherapy and rarely with radiotherapy. The Stanford group has convincingly shown that asymptomatic patients with non-bulky disease survive as long when watched and treated expectantly with single alkylating agents (for example, chlorambucil) as when treated intensively from diagnosis with drug combinations alone or together with wide field or whole body irradiation.^{20,21} Published prospective evidence suggests that as many as 60% of these patients may be managed in this fashion,²² the remainder requiring treatment for "B" symptoms, cosmetically unacceptable disease, or nodal masses interfering with vital structures (for example, ureteric compression). Such patients require treatment with a limited course of oral alkylating agents. Remission will occur in many cases, but relapse is inevitable when treatment is stopped (75% relapse by four years in one study).²⁰ The median survival has been seven to 10 years in most series.

Follicular mixed lymphoma is a biologically more aggressive disease. Long term remissions have been reported with combination chemotherapy,²³ but these results have not been reproduced.

Histological "transformation" to an intermediate grade tumour is common in patients followed for a long time. A change in the tempo of disease or disease refractory to previously effective treatment may be an indication for a fresh biopsy of accessible tissue and a change of treatment. The prognosis at this time will depend on the response to chemotherapy, but it is often poor in extensively pretreated patients.¹⁶

Follicular lymphoma is sensitive to treatment with interferon²⁴—but such treatment seems unlikely to play an important part in management since many less toxic treatments are available. Some patients have been treated with polyclonal or monoclonal antibodies^{3,4} directed at idiotype determinants on the surface of the tumour cells. There are anecdotal reports of regression, but most responses have been short lived. Nevertheless, research interest will clearly remain high.

Intermediate grade lymphoma

This group (comprising 40-45% of cases) includes follicular large cell, diffuse small cleaved cell, diffuse mixed, and diffuse large cell lymphomas. These diseases may arise at almost any site, or may evolve in a patient with a known low grade lymphoma—for example, follicular small cleaved subtype. Untreated, the disease is usually rapidly progressive. The management of nodal based diffuse large cell

lymphoma, the most common and most widely described subtype, will be described.

Diffuse large cell lymphoma is commonly B cell in origin but may be T or null cell.²⁵ Stage I presentation is rather more common in this disease than in the low grade lymphomas, occurring in roughly 15% of cases. The appropriate management of such early disease is controversial. Radiotherapy has proved successful in curing most patients,²⁶ but published series have included only small numbers of selected patients staged by laparotomy and treated with wide fields.

Chemotherapy alone has also been used for stage I disease (without staging laparotomy) with excellent results.²⁷ An alternative, which we have adopted, is to use clinical staging and treat low volume disease with radiotherapy to affected fields, reserving chemotherapy for bulky disease or relapse.²⁸ The choice of treatment will depend on local experience, the age of the patient, and the site and bulk of the disease.

Disease in stage II-IV disease should be treated soon after diagnosis with combination chemotherapy. These tumours are highly chemosensitive. Early regimens, devised 10-15 years ago—for example, CHOP²⁹—achieved complete remission of disease in roughly 60% of cases, with 35-40% long term survivors. Relapse after two years is uncommon but has been reported.³⁰ More recently several centres have described new regimens—for example, M-BACOD,³¹ MACOP-B³²—which have given over 80% complete remission rates and 60-70% long term survival. Regrettably no randomised clinical trials have compared these complex and toxic treatments with the earlier drug combinations. No definite role has emerged for radiotherapy in advanced disease.

Until recently drug resistant disease and relapsing disease had been associated with a dire prognosis. Recent experimental studies indicate that a few such patients may now be cured with high dose chemotherapy (with or without radiotherapy) with autologous marrow transplantation.³³ In some centres harvested marrow has been purged of tumour cells before reinfusion by the use of monoclonal antibodies.³⁴

Several other clinical problems may be identified in these patients. Spread of diffuse large cell lymphoma to the central nervous system (usually to the meninges) may occur, often as a complication of advancing disease resistant to drugs.³⁵ No clear place has been defined for prophylactic treatment of the central nervous system, but some centres give intrathecal methotrexate during chemotherapy to those at highest risk (patients with infiltration of the bone marrow). Another common problem is diffuse large cell lymphoma in the elderly.³⁶ In our experience such disease is common and rapidly progressive. Chemotherapy is often poorly tolerated, and selection of treatment is, therefore, difficult.

Few data are available to guide the clinician managing the other intermediate grade tumours. Certainly follicular large cell and diffuse mixed lymphoma should be managed in the same way as diffuse large cell lymphoma with comparable curative chemotherapy. Diffuse small cleaved lymphoma is also usually treated with combination chemotherapy, but after complete remission relapse commonly occurs over a relatively prolonged time scale.³⁷

High grade lymphoma

These tumours, which comprise 15-20% of cases, are among the most rapidly growing known in man. They include large cell immunoblastic lymphoma—which closely resembles diffuse large cell lymphoma—lymphoblastic

lymphoma, and small non-cleaved cell lymphoma (which includes Burkitt's lymphoma).

Lymphoblastic lymphoma is usually a T cell neoplasm which most commonly presents in young men with a mediastinal mass.³⁸ Early spread to the bone marrow and central nervous system are features of this disease, which histologically is indistinguishable from acute lymphoblastic leukaemia. The condition is always treated with intensive combination chemotherapy and prophylactic treatment should be given to the central nervous system. About 45% of patients may be cured.³⁸

Burkitt's lymphoma is a B cell neoplasm first described in Africa. A European/American form of this disease is now well recognised, though rare.³⁹ Staging should be limited, as chemotherapy is urgently indicated when this diagnosis is made. The acute tumour lysis syndrome (hyperkalaemia, hyperuricaemia, and hyperphosphataemia resulting from therapy) should be expected and prophylactic measures taken to prevent renal failure or death.⁴⁰ Central nervous system prophylaxis with intensive intrathecal chemotherapy is always indicated. This disease is curable, the cure rate relating to disease stage at presentation.

Other lymphomas

Malignant histiocytosis is a rapidly progressive lymphoma of young adults which is commonly associated with gross systemic symptoms. This disease is highly chemosensitive, and cure may be expected in some patients treated with a suitable drug combination.⁴¹ Malignant histiocytosis of the intestine is the lymphoma which most commonly arises in patients with coeliac disease.⁴² Recent studies suggest that the malignant cell is of T cell rather than histiocytic lineage.⁴³ The disease affects the bowel at multiple sites, and metastatic disease is common. In our experience this disease responds to chemotherapy, but survival is often short and complicated by perforation of the small bowel or haemorrhage or both.

Some T cell neoplasms have been recently described which do not easily fit into the working formulation. Adult T cell leukaemia/lymphoma associated with human T cell lymphotropic virus type I has been described predominantly in West Indians and the Japanese.⁴⁴ More common is the peripheral T cell lymphoma, which predominantly occurs in elderly men and is associated with a poor prognosis.⁴⁵

Extranodal lymphoma

Not uncommonly lymphomas arise primarily at extranodal sites. These tumours are usually of intermediate grade subtypes. Almost any organ may be affected,⁴⁶ common sites including the gastrointestinal tract (particularly stomach),⁴⁷ thyroid,⁴⁸ skin, breast, brain, or testis.⁴⁹ Staging should be carried out as for nodal lymphoma. Characteristically in some patients the disease remains confined to the site of presentation, and local treatment (surgery with or without radiotherapy) may suffice. Patients with more widespread disease must be treated with combination chemotherapy.

A discernible and ill understood tropism for specific extranodal sites is seen in some of these tumours. Examples include spread to the tonsil and stomach⁴⁷ or testes and nasopharynx⁴⁹ in individual patients. Possibly these lymphomas may be derived from mucosal associated lymphoid tissue ("mal-

tomas") and retain certain of the physiological characteristics of such cells (lymphocyte recirculation and homing).⁵⁰

Conclusion

Clinicians caring for patients with non-Hodgkin's lymphoma are working on a stimulating and rapidly progressing subject. The future holds great promise. The basic scientists are leading the way to greater understanding, and the challenge for physicians is to match these advances and translate them into improved results of treatment.

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G M MEAD

Consultant medical oncologist

J M A WHITEHOUSE

Professor of medical oncology
and director of Wessex
Regional Medical Oncology Unit

CRC Medical Oncology Unit,
Southampton General Hospital,
Southampton SO9 4XY

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