Non-Hodgkin's lymphoma. II: Management problems

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This is the ninth in a series of articles examining recent developments in cancer

In the first of our articles on non-Hodgkin's lymphoma we discussed identification, staging, and basic management.¹ In this article we discuss some of the conditions which present management problems and appropriate treatment of special and rare lymphomas.

Problems in treating aggressive lymphomas

ELDERLY PATIENTS

Lymphomas are primarily diseases of older patients; 60% of all patients are aged 60 or more. Some newly diagnosed patients are either too old or too frail to undergo the aggressive treatment regimens used in younger patients. Older patients experience greater toxicity, a worse outcome, and are underrepresented in reported clinical trials in diffuse large cell lymphoma.

In general, older patients should be treated with curative intent unless they have a serious intercurrent illness that precludes combination chemotherapy. Treatment must be tailored to fit their age and stage of disease. Patients with limited stage disease will usually tolerate the standard brief chemotherapy with or without radiotherapy which is appropriate for all patients and all ages.¹

Patients presenting with advanced stage disease may be treated either with CHOP (cyclophosphamide, vincristine, procarbazine, and prednisone) protocols in which doses are modified initially and then adjusted according to toxicity as described by the Nebraska Lymphoma Group² or with protocols developed specifically for older patients. We have reported on two regimens specifically designed for patients aged over 65, low dose ACOP-B (cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin) and VABE (vincristine, doxorubicin, bleomycin, etoposide, prednisone),³ and more recently have evolved an even briefer five treatment, eight week regimen called POCE.⁴ The results with this treatment programme are similar to those seen with the two previous regimens and the treatment is briefer. Five year survival of 133 patients treated with any one of these three regimens designed for older patients was 38%, which compares favourably with the 44% survival achieved in patients aged 60 to 70 years treated with our centre's aggressive protocols for younger patients. Giving more aggressive treatment to older patients has not been shown to yield a significant improvement in survival and can cause excessive toxicity. As patients aged 60-70 do not seem to have a much better outcome with more aggressive treatment we are reassured that our specially designed programmes are not undertreating older patients.

FOLLICULAR LARGE AND DIFFUSE SMALL CLEAVED CELL LYMPHOMA

These uncommon lymphomas are usually grouped with the aggressive histology lymphomas and often are also managed in the same way. Unfortunately, their clinical behaviour is not as consistent as that of other large cell lymphomas and the outcome is often similar to that in low grade disease, in which patients follow a chronic relapsing pattern. Management of these diseases is best designed for the individual and the patient should be treated according to the pre-existing

clinical course. In younger patients treatment as for aggressive histology lymphoma is reasonable, but in older patients, in whom the disease often follows an indolent course, expectant management or alkylating drugs are appropriate.

DISCORDANT, TRANSFORMED, AND COMPOSITE LYMPHOMAS

In patients with discordant lymphomas, both aggressive histology disease and low grade disease are detected in separate areas—for example, small cleaved cell lymphoma in the bone marrow and simultaneous large cell lymphoma in a peripheral lymph node. Transformed lymphoma is an aggressive lymphoma developing in a patient with a pre-existing history of low grade lymphoma. Composite lymphoma is the coexistence of an aggressive lymphoma and a low grade lymphoma in the same site (usually a lymph node). These three examples of two separate types of lymphomas coexisting in the same patient should not be confused with the mixed large and small cell lymphomas in which a single histological subtype contains two different sized malignant cells. The guiding principle in managing discordant, composite, and transformed lymphomas is to try to eradicate the most aggressive component of this disease since this constitutes the greatest threat to survival. Thus, treatment is usually the same as described for large cell lymphoma.¹

Newly diagnosed patients with discordant or composite lymphomas generally have a favourable short term prognosis, similar to that for patients with only large cell disease. Nevertheless, if patients survive the aggressive component of their disease they remain at risk of having the indolent component slowly re-emerge. The prognosis in patients with a transformed lymphoma depends both on the usual prognostic factors (age, stage, performance status, bulk of disease, etc) and on the extent and toxicity of earlier treatment for the low grade disease. Patients who have been heavily pretreated or have low grade disease that is refractory to chemotherapy are unlikely to tolerate or respond to aggressive treatment. In these circumstances treatment should be tailored to the individual and given with palliative intent.

Special sites of lymphoma

GASTROINTESTINAL LYMPHOMA

Gastrointestinal lymphomas may be complicated by a haemorrhage or perforation of a stomach or intestinal tumour in up to 25% of patients.^{4,5} In addition, the rapid liquefaction of a treated lymphoma may expose blood vessels or result in a full thickness perforation of the bowel wall. Either of these life threatening problems may occur at any time during treatment and require surgical intervention.

If a patient has a localised resectable gastrointestinal tumour a laparotomy and complete resection should be attempted. This facilitates diagnosis and debulking and avoids the complications of haemorrhage or perforation. Surgery is contraindicated if the patient is too frail or if complete resection of the tumour is either technically impossible or would be so extensive as to

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compromise the patient's nutrition or unduly delay systemic treatment. As a rule total gastrectomy or major small bowel resection that would result in the short bowel syndrome should be avoided. Patients who are malnourished because of gastrointestinal lymphoma may require intravenous hyperalimentation while being treated.

After resection, or if resection is not feasible, patients should be treated as described for either advanced stage or limited stage disease.¹ Chemotherapy is mandatory for all such patients who have large cell lymphoma. All patients with local gastrointestinal lymphoma should have a detailed ear, nose, and throat examination to rule out occult disease. There is about a 20% risk of Waldeyer's ring also being affected, and this may indicate the need for extensive treatment.

HEAD AND NECK DISEASE

All patients with affected tonsils, adenoids, pharynx, or tongue should have a complete contrast study of the stomach and intestine to detect gastrointestinal disease (figs 1 and 2). About 20% of patients presenting with primary disease of Waldeyer's ring will have occult gastrointestinal disease.

If paranasal or basilar skull sinuses are affected there is an increased risk that the central nervous system will be affected.⁵ This risk may be as high as 50% and necessitates prophylaxis. In patients with localised large cell lymphoma of the sinuses one practical approach is to give treatment in three phases: brief chemotherapy, followed by radiation of the affected site, and finally intrathecal chemotherapy.

TESTICULAR LYMPHOMAS

The incidence of testicular lymphoma increases with age, becoming the most common testicular malignancy in men over 60. In general, lymphomas at this site are treated according to stage except that the scrotum should always be irradiated as there is a high risk of bilaterality and the testis may act as a sanctuary from cytotoxic drugs.

CENTRAL NERVOUS SYSTEM LYMPHOMA

Lymphoma may affect the leptomeninges or parenchyma of the brain, in isolation or as part of systemic disease. Leptomeningeal metastases occur with variable frequency depending on the other sites of disease; the risk is highest with paranasal sinuses (50%) and bone marrow disease (10-20%) in patients with intermediate or high grade lymphoma. Lepto-

meningeal disease is extremely rare in patients with low grade lymphoma.

Patients with established leptomeningeal disease have a poor prognosis but occasionally can be cured. An Ommaya reservoir connected by a catheter to a lateral ventricle facilitates the giving of intrathecal chemotherapy with methotrexate or cytosine arabinoside, or both. We usually give chemotherapy until at least six treatments beyond a complete cytological remission in the cerebrospinal fluid.

As patients with affected paranasal sinuses, peripheral blood, or bone marrow are at increased risk of spread to the meninges they should receive prophylactic intrathecal chemotherapy. One approach is to give six doses, two each week, after the systemic disease has completely responded to treatment. This approach often has cumulative toxicity with concurrent systemic chemotherapy and must be given with care.

Primary lymphoma of the brain is rare (1% of all lymphomas). In most cases the histology is aggressive—usually large cell or small non-cleaved cell. This presentation of lymphoma is commonly seen in association with HIV infection or organ immunosuppression after transplant and in these cases is probably related to Epstein-Barr virus. Presentation is often insidious and this disease may easily be misdiagnosed in elderly patients. Systemic disease is rare when the initial presentation is a mass lesion in the brain.

The prognosis is poor despite an initial response to corticosteroids and radiotherapy and most patients succumb within one year of diagnosis, either from recurrent tumour or from neurological complications of the disease and its treatment. Overall, the two year disease free survival is less than 20%, and it is unclear whether systemic chemotherapy improves the prognosis for patients with primary brain lymphoma. The outcome for patients with AIDS remains even poorer and treatment is often palliative.

LYMPHOMA ASSOCIATED WITH AIDS

Patients with AIDS have an increased risk of developing aggressive lymphomas (usually large cell, immunoblastic, or small non-cleaved cell types). It is reasonable to screen patients presenting with these subtypes of lymphoma for HIV infection. Knowledge of infection is useful in planning treatment, estimating prognosis, and managing infectious complications. In addition, knowledge of the prevalence of AIDS in the population of patients treated for lymphoma is essential in interpreting the results of clinical trials since these patients generally have a worse outcome and experience more toxicity.

Although a few patients with AIDS related lymphomas may achieve a sustained complete remission, unfortunately, almost all patients eventually die of either the malignancy or AIDS related complications. At present the median survival of such patients is less than six months. Nevertheless, patients with AIDS who do not have a history of previous severe opportunistic infection and whose performance status is good may respond well to chemotherapy and achieve durable remissions. Optimal treatment should be delivered as long as tolerance is adequate. In general, however, treatment of AIDS related lymphomas remains palliative because of the poor prognosis of the underlying infectious disease.

RECURRENT LARGE CELL LYMPHOMA

Even the most effective treatment regimens for large cell lymphoma only cure about 50-60% of patients with advanced stage disease. Patients who are refractory to treatment or relapse after treatment often require further chemotherapy or radiotherapy. Several salvage regimens such as IMVP-16 (ifosfamide, methotrexate, etoposide),⁷ MIME (methyl gag, ifosfamide, metho-

FIG 1—Neck of patient with non-Hodgkin's lymphoma. Site of biopsy visible

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FIG 2—Non-Hodgkin's lymphoma of tonsils

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trexate, etoposide)⁸ and DHAP (cisplatin, cytosine arabinoside, dexamethasone)⁹ have been developed and produced some long term survivors. However, patients often relapse again and only a few achieve durable remission. Similarly, bone marrow transplantation protocols developed for relapsing diffuse large cell lymphoma induce high response rates, but less than 20% of patients achieve durable disease free survival.¹⁰ Only a few patients even proceed to such aggressive treatments and the overall outcome for relapsing patients with diffuse large cell lymphoma remains very poor.

Clearly, further research is needed on the initial management of patients identified as having poor prognostic factors if a higher cure rate is to be achieved in the initial treatment of aggressive lymphoma.

Special lymphomas

These are uncommon, rapidly proliferative diseases which constitute less than 10% of all lymphomas. They require intensive treatments similar to that used for acute leukaemia, including prophylactic treatment of the central nervous system.

LYMPHOBLASTIC LYMPHOMA

This is a disease usually seen in children or young adults (median age 17 years). It is twice as common in males as females, onset is usually rapid, a mediastinal mass is common, and B symptoms and bone marrow or central nervous diseases are often found. Malignant cells are usually, but not invariably, phenotypically T cell.

Coleman *et al* have developed a predictive model based on the results with multiagent chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone, L-asparaginase, central nervous system prophylaxis, methotrexate, and mercaptopurine).¹¹ This identifies patients with a good prognosis (bone marrow not affected, normal lactate dehydrogenase concentration), who have an 80% cure rate, and a second group with a poor prognosis, in which only 20% are cured. In our experience the overall outcome for all young patients presenting with this diagnosis is not as good as that reported by Coleman *et al*. Very aggressive initial treatment including upfront autologous or allogeneic bone marrow transplantation is valid for this disease. Further experimental treatments need to be tested in these patients to establish standard management.

SMALL NON-CLEAVED CELL LYMPHOMA

Small non-cleaved cell lymphoma is also labelled as diffuse undifferentiated lymphoma in the Rappaport classification. It is a B cell neoplasm which is highly

mitotic and rapidly proliferative. The age distribution is biphasic; the Burkitt type is seen more often in younger patients and the non-Burkitt type more often in older patients. Abdominal or gastrointestinal presentations are typical. These diseases are potentially curable when found in early stages but are difficult to eradicate in more advanced stages in the adult population. Although these lymphomas usually respond to high dose chemotherapy with alkylating drugs such as cyclophosphamide, rapid expression of drug resistance, relapse, and death often result.

Regimens similar to that reported by the United States National Cancer Institute are usually used for treating small non-cleaved cell lymphomas of both varieties.¹² No satisfactory treatment for the majority of patients with bulky disease has been identified. Such patients should be referred to institutions where new approaches are being investigated. Again high dose chemoradiotherapy and bone marrow transplantation in first remission should be considered in younger patients.

Although lymphoblastic lymphoma and small non-cleaved cell lymphoma arise from different lymphocyte cell lines (T and B respectively) and although there are important variations in the regimens used to treat them, they have some important features in common. Patients are at high risk of the acute tumour lysis syndrome when initially treated, especially those who have bulky disease or already impaired renal function. This may cause death from cardiac arrest secondary to the metabolic consequences of hyperuricaemia, renal failure, hyperkalaemia, hyperphosphataemia, and hypocalcaemia. All patients should be pretreated with allopurinol and sodium bicarbonate, a high fluid output should be established before treatment, and preparation should be made for haemodialysis in patients thought to be at risk of renal failure (particularly patients with a raised lactate dehydrogenase concentration). Central nervous system and bone marrow disease are common in both lymphomas and central nervous system prophylaxis is indicated. Small non-cleaved cell lymphoma is the most common lymphoma seen in immunosuppressed patients such as those with AIDS, organ transplants, or congenital immunodeficiency. Treatment of such patients is complicated by the underlying immunodeficiency and is seldom successful without correction of that defect. Recipients of organ transplants may also develop lymphoma-like lymphoproliferations which may resolve on withdrawal of immunosuppressants.¹³

Miscellaneous lymphomas and related conditions

The following lymphoproliferative malignancies are reviewed briefly in order to place them in context relative to the malignant lymphomas.

B CELL NEOPLASMS

Chronic lymphatic leukaemia is an indolent disease, typically occurring in elderly people and associated with long survival. It is morphologically indistinguishable from small lymphocytic lymphoma and is managed in the same way.

Waldenström's macroglobulinaemia is the plasma-cytoid variant of small lymphocytic lymphoma and is associated with an IgM paraprotein. Management is as for small lymphocytic lymphoma. Patients with this variant may develop symptomatic hyperviscosity. This is usually best managed with plasmapheresis and institution of chemotherapy with an alkylating drug such as cyclophosphamide or chlorambucil.

Multiple myeloma is a malignancy of mature plasma cells which primarily affects bones and bone marrow and is usually associated with a monoclonal gammopathy in the blood or urine. The clinical course is often

Management problems in patients with non-Hodgkin's lymphoma

- Elderly patients with aggressive lymphomas experience greater toxicity and a worse outcome from treatment
- Gastrointestinal lymphomas may be complicated by haemorrhage or perforation
- In testicular lymphoma the scrotum should always be irradiated because of a high risk of bilateral disease and the possibility of the testis acting as a sanctuary from cytotoxic drugs
- Even the most effective regimens for large cell lymphomas cure only about a half of patients with advanced disease
- The acute tumour lysis syndrome, which follows initial treatment particularly of bulky tumours, may result in death from the metabolic consequences of hyperuricaemia, renal failure, hyperkalaemia, hyperphosphataemia, and hypocalcaemia

complicated by bacterial infections, renal disease, hypercalcaemia, pancytopenia, and localised bone destruction. This disease is usually treated with oral alkylating drugs and prednisone with irradiation of focally symptomatic bone lesions.

Intermediate cell lymphocytic lymphoma has cytological features between those of small lymphocytic (well differentiated) and small cleaved cell (poorly differentiated) lymphoma and includes so called "mantle zone" lymphoma.¹³ Typically, patients present with advanced disease and may have a shorter survival than patients with low grade lymphoma. The nodal architecture is usually, but not invariably, diffuse. These patients are best managed in the same manner as those with diffuse small cleaved cell lymphoma. Mantle zone lymphomas are intermediate cell lymphomas in which the malignant cells proliferate in wide mantles around germinal centres that appear normal. They are a follicular variant of intermediate lymphocytic lymphoma and usually are more aggressive than small cleaved cell lymphomas. In the working formulation intermediate cell and mantle zone lymphomas are usually included in the small cleaved cell or mixed cell categories and are not separately described. A better definition and more reproducible identification of these uncommon lymphomas will improve our understanding of their natural course.

T CELL NEOPLASMS

Mycosis fungoides and its variant, the Sézary syndrome, are rare cutaneous T cell lymphomas which may resemble eczema or psoriasis in early presentation. These diseases usually progress gradually to formation of plaques and tumours after a phase of increasingly extensive erythroderma. Mycosis fungoides pursues an indolent course with a median survival of eight years. Patients should be managed in a specialised centre by experienced doctors. Treatments include whole body electron beam radiotherapy, topical nitrogen mustard, and photochemotherapy. Systemic treatment with all alkylating drugs and prednisone may be of some benefit and some studies have reported benefit with interferon.¹⁴

T cell chronic lymphatic leukaemia is a rare variant (2% of this usually B cell disease). It often follows in a rapidly progressive course.

Peripheral T cell lymphomas are a clinically and morphologically heterogeneous group of lymphomas. About 10-20% of all lymphomas are T cell in origin.

Peripheral T cell lymphomas are represented in several categories in the working formulation, including diffuse small cleaved cell, diffuse mixed, diffuse large cell, and immunoblastic subtypes. Patients often present with advanced disease. Bone marrow disease, hypercalcaemia, and eosinophilia are relatively common. A poor prognosis has been reported, but this is not universally accepted as other prognostic factors such as age, stage, and performance status were not adjusted for.

The spectrum of T cell lymphomas seen in Japan is similar to that of the peripheral T cell lymphomas described above. Not unexpectedly, these lymphomas are often associated with peripheral adenopathy, hypercalcaemia, and leukaemia. The prognosis is reported to be poor, with early appearance of disease refractory to intensive chemotherapy.

ANGIOIMMUNOBLASTIC LYMPHADENOPATHY

This abnormal lymphoproliferative disease, although not histologically a malignancy, has a rapidly progressive, often fatal course. Treatment usually consists of high dose prednisone, which should be used to maximum response then tapered. Patients whose condition cannot be maintained without prednisone should have a trial of cyclophosphamide 50-100 mg/m² orally every other day, a maintenance immunoregulatory dose which can be continued for long periods if necessary. Many patients with angioimmunoblastic lymphadenopathy develop immunoblastic lymphoma, which if discovered should be treated appropriately.

Conclusion

Although malignant lymphomas are highly treatable, many problems still remain to be addressed in the 1990s. The main topics of interest will be improved treatment and, if possible, cure of advanced stage low grade lymphomas; better identification of patients with intermediate and high grade lymphomas who have a poor prognosis to allow more aggressive and effective treatment; and better management of patients relapsing after first treatment.

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