Non-Hodgkin’s lymphoma in the elderly

The incidence of non-Hodgkin’s lymphoma (NHL) is increasing, and this increase is even more rapid in the older population. Although treatment of NHL in the elderly is sometimes planned with curative intent, more often the aim is to prolong life with minimal symptoms from disease or therapies. Dr Clare Rowntree discusses the two most common forms of NHL seen in this group and reviews management options.

Non-Hodgkin’s lymphomas (NHLs) are a heterogeneous group of tumours of the lymphoid system. The majority (90 per cent) of NHLs arise from B-cells and the remaining 10 per cent arise from T-cells. The incidence of NHL is increasing in both Europe and the US at 5–10 per cent per year, with the current incidence being 12–15 cases per 100,000.1 The reasons for this increase are unclear at the present time. The incidence in the elderly is increasing even more rapidly which, taken with an ageing population, has significant implications for future planning of haemato-oncology services.

Clinical presentations of lymphoma vary due to the multisystem nature of the disease. Lymphadenopathy is a common presenting feature but the disease can present in many guises from solid tumours in sites such as the orbit, to skin lesions, to non-specific symptoms of fever and weight loss. To make a diagnosis of lymphoma, a biopsy of involved tissue is always required. Classification of the type of lymphoma, according to the Revised European-American Classification of Lymphoid Neoplasms (REAL)², can be difficult and review by a specialist haemato-pathologist is usually required. Once a diagnosis of lymphoma has been made it is important to make an assessment of the aggressiveness of the lymphoma, the extent of disease, and the patient’s prognosis.
and possibilities of cure. A management plan can then be formulated within the setting of a lymphoma multidisciplinary team (MDT), which will have a core membership of radiation oncologists, haematology-oncologists, pathologists, radiologists, palliative care specialists and clinical nurse specialists. In the elderly, treatment may be planned with curative intent, but more frequently the aim will be to achieve a prolonged life expectancy with minimal symptoms from disease or therapies.

**Diffuse large B-cell lymphoma**

Diffuse large B-cell lymphoma (DLBCL) is classed as a CD20 (surface marker found on B-cells) positive aggressive lymphoma. It is the most commonly diagnosed lymphoma, accounting for 40 per cent of new cases. Of these new cases, more than 50 per cent occur in patients over 60 years of age – making the elderly the largest group of patients with this disease. DLBCL is classified as an aggressive lymphoma because survival is limited due to disease in the absence of effective therapy.

At presentation, approximately 75 per cent of all patients with DLBCL will have widespread disease and this percentage is higher in the elderly. In order to try to predict prognosis at diagnosis, the *International Prognostic Index* (IPI) was published in 1993. Five independent variables were identified as being important negative predictors for survival:

- age over 60 years;
- performance status (Eastern Cooperative Oncology Group scale);
- a raised lactate dehydrogenase level;
- involvement of two or more extranodal sites;
- stage of disease.

A higher score predicts an increased risk of death due to lower remission rates and increased relapse rates. The IPI illustrates why the elderly diagnosed with DLBCL have had a poorer outlook than their younger counterparts.

For many years the gold standard chemotherapy regimen used to treat DLBCL has been cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) given every 21 days. Historically, six to eight cycles of CHOP resulted in cure in approximately 40 per cent of patients, although figures were lower in the elderly. Clinicians often have concerns about delivering CHOP-like regimens to them as it is well documented that when treated with chemotherapy for lymphoma they appear to be more susceptible to neutropenic sepsis, particularly during early cycles of treatment. Not only are neutropenic infectious complications more common in the elderly, they are also more severe. Patients over 65 are hospitalised more frequently for febrile neutropenia following CHOP, require longer stays in hospital and have increased mortality. In the past this has often lead to clinicians reducing doses of chemotherapy or changing to non-anthracycline containing regimens. It has been suggested that downgrading treatment is the main reason for the traditionally inferior outcomes seen within this age group.

Over recent years, two important studies have had a major impact on treatment of DLBCL in the elderly. The first was from *Groupe d’Etude des Lymphomes de l’Adulte* (GELA), where patients between the ages of 60 and 80 years with advanced DLBCL were randomised to receive CHOP or CHOP plus rituximab – a chimeric (human-mouse) anti-CD20 monoclonal antibody. The addition of rituximab to CHOP chemotherapy resulted in significantly superior disease-free and overall survival. The two-year disease-free survival rose from 40 per cent to 58 per cent with no significant increases in toxicity. The survival benefit was seen in all patient groups and was not dependent on the presenting IPI score.

The German non-Hodgkin’s study group also looked at patients over 60 years with DLBCL. They showed that increasing the intensity of CHOP to a 14-day schedule also significantly improved survival. However, the toxicity of this approach in the elderly was increased.

From these data, it has become clear that many elderly patients should be treated in the same way as younger patients – ie, with curative intent. Rituximab-CHOP has now become the gold standard first-line therapy for DLBCL in all patients up to 80 years within the UK.

Patients over 80, or those with a poor biological age (their physical age as opposed to their actual age), should be considered as having incurable disease for the most part and the emphasis should be placed on life prolonging treatment with minimal toxicity. Conventional therapy may not be feasible or appropriate in this age group, and time must be taken with the patient to discuss their options fully. Rituximab-based regimens, such as rituximab with cyclophosphamide, vincristine and prednisolone...
(CVP), are usually considered for this age group although single agent chemotherapy for symptom control may be more appropriate. Shared care between hospital teams, general practitioners and community palliative care teams can be very beneficial in this often frail group of patients.

**DLBCL in relapse**

Relapse of DLBCL in the elderly is typically widespread and often associated with a poor performance status. The only curative option for relapsed DLBCL at the current time is aggressive salvage chemotherapy consolidated with high dose therapy (HDT) and autologous stem cell transplantation. The only data from randomised trials verifying this approach are in young patients\(^1\). However, in the minority of elderly patients who otherwise have a good performance status and chemosensitive disease, HDT should be considered as an option. For all other elderly patients, the possibility of cure with second-line therapies is very low\(^2\). In this group a palliative approach may be offered, at which time quality of life and patient choice should be of prime concern. Further chemotherapy, either single agent or combination, is frequently used. The aim of this is a second remission or, more simply, symptom control. Radiolabelled anti-CD20 antibodies have been shown to induce responses in 44 per cent of patients with DLBCL at relapse and can be given with minimal side effects\(^3\). However, at the current time, these are not routinely available in the UK outside of a clinical trial.

**Follicular lymphoma**

Follicular lymphoma (FL) is also a CD20 positive B-cell lymphoma, and it is the second most frequent type of NHL in the UK. The prognosis of patients with FL is broadly linked to the extent of the disease.

Unfortunately, the majority of patients will have widespread disease at diagnosis. However, 15–20 per cent of patients will have truly localised disease at presentation and the treatment of choice is radiotherapy. This will give long-term disease-free survival in approximately 45 per cent of patients\(^4\). The remaining patients have essentially incurable disease.

Despite various advances in treatment of FL over the past decade, the prognosis remains largely
unchanged with the average life expectancy being 8–10 years\textsuperscript{14}. The course of FL is characterised by initial responses to treatment followed by relapse. FL is classed as an indolent lymphoma, but approximately one-third will transform to a high grade lymphoma and this event is usually associated with a very poor outcome. Age over 60 years is again a predictor of decreased survival in FL\textsuperscript{15}. There are no specific FL trials in the elderly and a broad range of therapeutic options are available, ranging from a ‘watch and wait’ approach to a reduced intensity allogeneic stem cell transplant. These options are outlined below.

**Watch and wait**

It is well documented that as many as 25 per cent of tumours in patients with untreated FL will undergo spontaneous regression\textsuperscript{16}. With a ‘watch and wait’ policy, the median time until chemotherapy is required is three years. No overall differences in survival have been observed when treatment is delayed compared with patients treated with conventional chemotherapy at the outset. For patients over 70 years, the chances of either requiring chemotherapy or dying of FL at 10 years are 40 per cent\textsuperscript{17}. Consequently, it has long been acceptable to adopt a ‘watch and wait’ policy for patients who do not have systemic symptoms from their disease or signs of major organ compromise and do not have a high tumour burden. The pros and cons of a ‘watch and wait’ policy must be carefully explained to the patient. Even with adequate support, some patients find this approach unacceptable and will opt for early treatment.

**First-line therapy for FL**

Rituximab has also been extensively investigated in patients with FL and has shown to be highly effective. As a single agent it is very well tolerated and induces responses in 67 per cent of de novo patients\textsuperscript{18}. Consequently the British National Lymphoma Investigation group are currently running a trial comparing ‘watch and wait’ with single agent rituximab at diagnosis. The results of such trials are eagerly awaited.

Many trials have compared combination chemotherapy with or without rituximab in first-line therapy for advanced stage FL. Most have shown a significant increase in response rates and progression-free survival with the addition of rituximab. Whether these improved outcomes will translate into prolonged survival is not yet clear. The improvements in responses occur in both chemotherapy naive and previously treated patients. Based on these data, many haematologists will now use CVP in combination with rituximab as first-line therapy in the UK\textsuperscript{19}.

**Relapse of FL**

When FL relapses, the median survival for a patient is four and a half years. There are some emerging data suggesting that HDT with autologous stem cell rescue or an allogeneic stem cell transplant with reduced intensity conditioning may offer the possibility of long-term disease free-survival in patients with relapsed disease\textsuperscript{20}. While these procedures are too toxic for many elderly patients, they may be appropriate for occasional patients who lack other poor risk features and have a good performance status.

For all other patients, the emphasis should be on attaining a sustained second response with minimal toxicity. These patients should all be discussed and treated within a lymphoma MDT setting. Options include a further period of ‘watch and wait’, second-line chemotherapy regimens or monoclonal antibody therapies. Results with radiolabelled monoclonal anti-CD20 antibodies are very encouraging in this group of patients, with 60–80 per
The challenge facing us all will be to provide adequate support to older patients undergoing increasingly toxic regimens. Faced with an ageing population and an increasing incidence of lymphoma, we will need to organise our resources so we are able to offer curative treatment to those where we can. However, cure is still not an option for the majority of elderly patients with lymphoma. For these remaining patients we must strive to provide high quality, multidisciplinary based care, that achieves a good quality of life with minimal side effects from our therapies.

**Conflict of interest: none declared.**

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**Key points**

- The incidence of lymphoma is increasing within the elderly population.
- With more intensive therapies, the survival rates in elderly patients with NHL are approaching those in younger patients.
- The recent addition of novel antibody therapies to conventional chemotherapy has made dramatic improvements to survival in elderly patients with DLBCL.
- All patients with lymphoma should be cared for within the lymphoma MDT setting.

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**References**