The management of lymphomas involves a range of different chemotherapy schedules, with novel medicines emerging and offering better treatment options

Lymphomas: current and future treatment options

By Nick Duncan

The management of Hodgkin lymphoma and non-Hodgkin lymphoma is broadly similar and is based on combination chemotherapy. In Hodgkin lymphoma, the overall aim is to maximise the likelihood of cure, while minimising both short and long-term toxicities.

The management of non-Hodgkin lymphoma depends on the subtype. In aggressive lymphomas, the aim of treatment is to cure the patient, while in indolent forms treatment may not be required for several years.

**Classic Hodgkin lymphoma**
Chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) has been the cornerstone of treatment for all stages of classic Hodgkin lymphoma for the past 30 years (see ‘Common chemotherapy schedules for Hodgkin lymphoma’)\(^1\). This is followed, in some instances, by localised radiotherapy.

A recent study found that, for patients with limited stage disease (see accompanying article), two cycles of ABVD are as effective as four cycles\(^2\). Radiotherapy is often used in practice, although there is an ongoing debate as to whether it can be safely omitted in patients who have achieved a complete metabolic response — as assessed by positron emission tomography (PET) scan — with chemotherapy alone (see PET scans).

ABVD is the standard approach in the UK for patients with intermediate-stage disease. However, a large German study demonstrated improved progression-free survival with an intensive escalated BEACOPP regimen (see ‘Common chemotherapy schedules for Hodgkin lymphoma’) in combination with ABVD\(^3\). However, no increase in overall survival was shown.

Patients with advanced stage disease are generally treated with chemotherapy alone, with radiotherapy being reserved for the management of residual disease. There is a lack of consensus as to whether ABVD or escalated BEACOPP is the most appropriate chemotherapy schedule. A recent meta-analysis demonstrated a 10% survival advantage at five years with the more intensive escalated BEACOPP schedule\(^3\). However, it is regarded as being more toxic than ABVD, and is generally only considered for patients younger than 60 years with high risk disease as defined by a high Hasenclever International Prognostic Score (See accompanying article).

Depending on their stage of disease at diagnosis, between 10% and 40% of patients with Hodgkin lymphoma will either fail to respond to their initial chemotherapy or (more commonly) relapse after their treatment has been completed.

A variety of chemotherapy regimens are widely used for such patients, which often include platinum-based medicines such as cisplatin and carboplatin. There are no randomised trial data to demonstrate if any schedule is more effective than another\(^5\).

Patients who respond to second-line chemotherapy are subsequently treated with high-dose chemotherapy followed by an autologous stem cell transplant (ASCT), provided the patient is fit enough to tolerate this more intensive approach. The most widely used chemotherapy regimen in the UK is BEAM (see ‘Common chemotherapy schedules for Hodgkin
lymphoma), which was first shown to be effective for relapsed Hodgkin lymphoma in the early 1990s6. Brentuximab is a novel immunoconjugate used for patients who relapse after ASCT. It is a monoclonal antibody (that targets the antigen CD30) bound to monomethyl auristatin E, which inhibits the polymerisation of tubulin but is too toxic to be used on its own. Brentuximab was licensed in the UK in 2013 and is currently being reviewed by the National Institute for Health and Care Excellence (NICE) as an option for people with CD30-positive Hodgkin’s lymphoma who have relapsed or are at high risk of relapse following ASCT.

One trial investigated the use of brentuximab in 102 patients with relapsed or refractory Hodgkin lymphoma, who received up to 16 doses of the drug as a short intravenous infusion every 21 days7. The overall response rate was 75%, and 34% of patients achieved a complete remission. The median progression-free survival was 5.6 months, and more than 20 months in patients who achieved a complete remission. Tolerability was generally good, and the most common adverse effects reported were peripheral sensory neuropathy, nausea, fatigue, neutropenia and diarrhoea.

There is also interest in using brentuximab as a first-line treatment for Hodgkin lymphoma, based on promising results from a study which combined it with AVD (there is a high risk of pulmonary toxicity when brentuximab is given in combination with bleomycin)8. However, the significant cost associated with treatment means brentuximab is unlikely to become a standard treatment in the UK.

Brentuximab is also licensed as a treatment for anaplastic large cell lymphoma, a form of T-cell lymphoma known to express the CD30 antigen.

Other novel treatment options are currently being investigated for relapsed Hodgkin lymphoma. These include: everolimus, an mTOR (mammalian target of rapamycin) inhibitor already being used to treat breast, hepatocellular and renal cell cancer; panobinostat, an oral histone deacetylase inhibitor that may have a synergistic effect with everolimus; and lenalidomide, an immunomodulatory agent with antiangiogenic effects8. Younger patients who relapse after ASCT may be treated with a reduced intensity conditioning (RIC) allogeneic stem cell transplant, which has been shown to cure some patients in this subgroup. RIC is less intensive than historical chemotherapy regimens used in transplants, and can be used in patients for whom conventional high dose chemotherapy would be too toxic.

There is currently a lack of clinical trial data to determine the effectiveness of this treatment option, but the UK Clinical Research Network Pilot of Allogeneic Immunotherapy in Refractory Disease (PAIReD) study is investigating the role of RIC allografting using the BEAM-Campath conditioning schedule.

**Nodular lymphocyte predominant Hodgkin lymphoma**

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a rarer subtype of the disease but is managed in a broadly similar way to classic Hodgkin lymphoma9. Ann Arbor stage 1 disease is usually treated with excision or radiotherapy alone. Malignant cells express the CD20 antigen in NLPHL, and rituximab, an anti-CD20 monoclonal antibody, can be given alone or in combination with standard chemotherapy as a first-line or second-line treatment. Importantly, NLPHL cells do not express CD30, so brentuximab is not used.
**Aggressive non-Hodgkin lymphoma**

The aim of treatment in aggressive forms of non-Hodgkin lymphoma, such as diffuse large B-cell lymphoma (DLBCL), is to cure the patient. Treatment is tailored to the patient, taking into account their age, co-morbidities and any risk factors. It usually involves six to eight cycles of R-CHOP chemotherapy, which adds rituximab to the CHOP schedule developed in the 1970s (see ‘Common chemotherapy schedules for non-Hodgkin lymphoma’) and has shown improved response rates compared with CHOP alone\(^9,10\). For example, a large French study of 399 patients aged 60–80 years demonstrated that the addition of rituximab to CHOP significantly improved five-year survival rates from 45% to 58%\(^{10}\).

R-CHOP is usually repeated every 21 days. Studies have investigated increasing the intensity of treatment to a 14-day cycle, but this was not found to be more effective than the standard 21-day cycle, was more expensive and increased the risk of toxicities such as thrombocytopenia\(^{11}\).

Other intensified regimens are also used, such as R-ACVBP\(^{12}\) (rituximab, doxorubicin, vindesine, cyclophosphamide, bleomycin, and prednisolone, given every 14 days) and dose adjusted (DA)-EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab)\(^{13}\), (DA)-EPOCH-R presents particular pharmaceutical challenges as it involves administering the vincristine, doxorubicin and etoposide together as a continuous IV infusion over 96 hours via a portable infusion pump.

High-dose chemotherapy followed by ASCT is sometimes used to improve outcomes following remission. However, there is mixed evidence as to whether this is effective, and it is considered an experimental treatment option\(^{12}\).

More than 30% of patients with DLBCL will either relapse or be unresponsive to treatment. For those patients who are fit enough for further intensive treatment, similar strategies to relapsed Hodgkin lymphoma are recommended, with chemotherapy regimens often involving platinum-based agents.

These treatments are followed by BEAM chemotherapy and an ASCT and then a BEAM chemotherapy. The prognosis for patients who have DLBCL refractory to treatment, an early relapse after first-line chemotherapy or a relapse after ASCT is poor. Some of these patients may be treated with an allogeneic stem cell transplant.

Those not fit enough for intensive second-line treatment may be treated with gentler chemotherapy schedules such as R-GEMOX (rituximab, gemcitabine and oxaliplatin)\(^ {14}\).

**Follicular lymphoma**

Follicular lymphoma often presents asymptomatically and does not always require immediate treatment. Treatment is usually reserved until the patient becomes symptomatic, which occurs a median of 2.5 years after diagnosis, but can be more than 10 years.

There is currently no evidence that survival is improved by early initiation of treatment in asymptomatic patients\(^{15}\). However, treatment with rituximab at diagnosis is currently being evaluated in clinical trials and, although it has yet to demonstrate an overall survival benefit, it does appear to improve progression-free survival rates\(^{16}\).

Patients who present with limited disease can be treated with radiotherapy alone, which may cure the lymphoma.

Symptomatic patients with more advanced disease are treated with chemotherapy and rituximab, which aims to prolong survival. Commonly used regimens include R-CHOP, R-CVP, FCR and R-bendamustine (see ‘Common chemotherapy schedules for non-Hodgkin lymphoma’).

R-bendamustine is increasingly being used as the

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**3: New developments in non-Hodgkin lymphoma**

- **Subcutaneous rituximab** is licensed in the UK for the treatment of patients with follicular lymphoma and diffuse large B cell lymphoma. All patients must have received at least one previous dose of intravenous rituximab. It is given as a 1,400mg dose and, as it requires 11.7ml to be injected, is formulated with hyaluronidase to aid administration. A recent NHS England Specialised Services Circular (SSC1434) stipulated that subcutaneous rituximab will only be funded for maintenance therapy and not if used in combination with chemotherapy.

- **Pixantrone** is an anthracyclene analogue similar to mitoxantrone, and has been approved by NICE as a third-line or fourth-line monotherapy for treating repeatedly relapsed or refractory aggressive non-Hodgkin lymphoma\(^ {22}\). This recommendation is based on results of an international phase III trial, which found improved response rates and progression-free survival (and a trend towards increased overall survival rates) when pixantrone was compared with standard therapy\(^ {23}\).

  - Pixantrone is given intravenously at a dose of 50mg/m\(^2\) on Days 1, 8 and 15 of each 28-day cycle for up to 6 cycles. It is less cardiotoxic than mitoxantrone, although the manufacturer recommends that left ventricular ejection fraction (LVEF) is monitored.

  - Ibrutinib, a novel oral Bruton’s tyrosine kinase (BTK) inhibitor, has received initial authorisation from the European Medicines Agency (EMA) for the treatment of both chronic lymphocytic leukaemia and relapsed or refractory mantle cell lymphoma.

  - BTK is a cytoplasmic enzyme that is an intermediary in B cell signalling pathways. It is indicated as a first-line or second-line treatment (in combination with rituximab) for chronic lymphocytic leukaemia, and as mono-therapy for relapsed follicular lymphoma.

  - A phase II study of idelalisib 150mg twice daily in 72 patients with follicular lymphoma, who had received at least two prior lines of therapy, found 54% of patients responded to treatment, with a median duration of response of more than 12 months\(^ {25}\).
The RATHL study, which is based in the UK, is currently investigating the role of interim positron emission tomography (PET) scans as a means of assessing patients’ risk of relapse and tailoring treatments accordingly. The study involves patients with intermediate or advanced stage Hodgkin lymphoma who received a PET scan after two cycles of ABVD chemotherapy. Patients with a negative scan have been randomised to a further four cycles of ABVD or four cycles of AVD (omitting the bleomycin, which is known to be associated with long-term lung toxicity). Patients with a positive PET scan have been switched to a BEACOPP regimen. To date the study has not published its findings.

**PET Scan**

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**Mantle cell lymphoma**

Mantle cell lymphoma is an indolent lymphoma but has a five-year survival rate of around 30% and is treated in a similar fashion to the more aggressive lymphoma subtypes.

The current gold standard for younger, fitter patients is a schedule of alternating R-MaxiCHOP (R-CHOP with cyclophosphamide 1,200mg/m^2 and doxorubicin 75 mg/m^2) and high dose cytarabine (the so-called ‘Nordic schedule’) followed by ASCT. The 10-year survival rate for patients treated with this regimen — which has only recently been introduced in the UK — is 58%, and overall survival rates for mantle cell lymphoma are likely to improve with time.

Another emerging option in patients with mantle cell lymphoma is the FCR (fludarabine, cyclophosphamide and rituximab) schedule, which has a better response rate and improved overall survival rate compared with fludarabine and cyclophosphamide alone.

**Burkitt’s lymphoma**

Historically, Burkitt’s lymphoma had a very poor prognosis. However, intensive inpatient chemotherapy regimens such as CODOX-M/IVAC (commonly with rituximab), outcomes have improved considerably. Patients with Burkitt’s lymphoma are at very high risk of tumour lysis syndrome. This is a medical emergency that occurs when chemotherapy causes large numbers of tumour cells to die over a short period. These cells release their cellular contents, leading to complications such as hyperkalaemia, hyperphosphataemia, hyperuricaemia, hypocalcaemia, acute uric acid nephropathy and acute renal failure. Although allopurinol is usually used to reduce the risk of tumour lysis syndrome, it is unlikely to be effective in patients with Burkitt’s lymphoma due to the very high number of cells killed, and intravenous rasburicase (0.2mg/kg/day for 5–7 days) is used instead.

R-CODOX-M/IVAC, a schedule that alternates rituximab, cyclophosphamide, vincristine, doxorubicin and methotrexate with a regimen including rituximab, etoposide, ifosfamide and cytarabine, can be considered for patients with diffuse large B cell lymphoma who have very high IPI scores (see accompanying article) and require a more intensive chemotherapy schedule than R-CHOP.

**References**