Diffuse large B-cell lymphoma – EML

The application sought the endorsement of medicines already included on the complementary list of the EML (cyclophosphamide, vincristine, doxorubicin and prednisone) for use in the "CHOP" regimen for diffuse large B-cell lymphoma. The application also sought the addition of rituximab to the core list of the EML, for use in combination with CHOP in the "R-CHOP" regimen. In settings where rituximab is not available or feasible, the application proposed that CHOP be the recommended fundamental regimen for this disease.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), constituting about 30% of all cases of NHL globally *(1)*. This subtype of cancer is heterogeneous and aggressive, yet scientific advances in the past quarter of a century have rendered it curable with chemotherapy or with combined chemotherapy and immunotherapy. Until 1998, the standard regimen for treatment of DLBCL included cyclophosphamide, vincristine, doxorubicin and prednisone (the CHOP regimen). The standard of care in Europe, the United States and other high-income settings now includes a combination of these four chemotherapy medicines plus immunotherapy with rituximab – the humanized monoclonal antibody directed at the CD20 antigen (the R-CHOP regimen). Research demonstrates 55.8% survival at 6 years among patients receiving CHOP only and 74.3% among patients receiving R-CHOP *(2)*. The chance of survival without chemotherapy is 0%. Thus, with the addition of CHOP alone, gains in survival go from 0% to 56%. Drugs comprising CHOP are all old, off-patent drugs, while rituximab remains on-patent, more costly and technically more difficult to administer. Adding rituximab to CHOP results in an average additional increase in long-term survival of about 20%. Since many patients are young this results in many life-years gained.

Public health relevance

Non-Hodgkin lymphoma is the most common type of lymphoma and DLBCL is the most common type of NHL. DLBCL is a fast-growing, aggressive form of NHL. It is fatal if left untreated but, with timely and appropriate treatment, approximately 70% of all patients can be cured. The incidence of DLBCL in the United States is approximately 7 cases per 100 000 population per year. The disease affects adults over 60 years of age to a greater extent, but it occurs in patients of all ages, including children *(1).* Although global epidemiological data on DLBCL burden are limited, the combined information generated by discrete studies and international estimates of the overall burden of NHL (e.g. GLOBOCAN 2012 *(3)*) warrants urgent action to expand access to chemotherapy and, where possible, immunotherapy.

The International Agency for Research on Cancer estimates the age-standardized incidence rate of NHL among both sexes worldwide to be 5.0 per 100 000 people. Data from GLOBOCAN 2012 show the age-standardized rate in more developed regions to be more than double that in less developed regions (8.6 and 3.6, respectively). However, it is plausible that this difference reflects differences in detection and diagnostic capacity. A similar scenario was observed in USA in the late 20th century: improvements in detection methods in the 1980s are considered to be one of the reasons for the significant increases in incidence during this period, which have since been followed by a plateau. A growing epidemic of human immunodeficiency virus (HIV) infection in USA at that time is also understood to have contributed to the increased incidence *(4)*. The difference in mortality rates between more and less developed regions of the world (2.7 and 2.3 per 100 000 respectively) is less pronounced than the difference in incidence *(3)*.

Research on DLBCL offers further insight into the impact of this disease in under-resourced parts of the world. A recent study reported on the burden of NHL subtypes in central and South America, analysing 1028 consecutive cases drawn from four academic medical centres and one private laboratory *(5)*. This research showed that DLBCL constituted 40% of all forms of NHL – a slightly higher proportion than that recorded in Europe and USA. A retrospective adult cohort analysis in Mashhad, Islamic Republic of Iran, analysed data on 391 patients and also showed DLBCL to be the most common subtype of NHL *(6)*. These studies, coupled with epidemiological data from GLOBOCAN, support the conclusions that the burden of DLBCL is not confined to high-income settings and that treatment options must be made available internationally.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Pathological analysis of surgically excised lymph node or extranodal tissue is required for diagnosis. If treatment with R-CHOP is possible, basic immunohistochemistry is required to detect the presence of the antigen CD20, located on the surface of the malignant B-lymphocytes, which is targeted by rituximab. A minimum diagnostic panel (where possible) should also include serum lactate dehydrogenase (LDH) (for International Prognostic Index (IPI) determination). When available, an enhanced diagnostic panel might include CD10, BCL6, MUM-1 to distinguish germinal centre and ABC subtypes of DLBCL.

Testing

It has been recommended that pretreatment tests include staging, using contrast-enhanced computerized tomography (CT), and blood counts and chemistries to assess critical organ function, including renal and hepatic function. The role of pretreatment cardiac assessment with echocardiography is uncertain: it is possible that it does not modify the treatment strategy or predict toxicities *(7)*. Hepatitis B and C status should be assessed and monitored closely if positive.

Administration and care of patients

Administration requires intravenous infusion capacity and regular patient access to clinical care. In developed countries, administration is usually performed in outpatient facilities; in other settings, patients may be treated in inpatient facilities. Intravenous hydration and antiemetics should accompany administration of both CHOP and R-CHOP. Doxorubicin and vincristine require care to prevent soft tissue extravasation, which can cause severe local reactions and necrosis. Rituximab can cause severe allergic reactions and must be given slowly, with close monitoring, and supportive medicines must be readily available, including adrenaline, steroids and antihistamines. Premedication with paracetamol 650 mg orally, hydrocortisone 100 mg IV, and diphenhydramine 25–50 mg IV 30–60 minutes before rituximab (at least before the first rituximab dose) is recommended and can be scaled back if there is no reaction to the first dose. If the patient has evidence of hepatitis B or C infection, this should be monitored since administration of rituximab can reactivate either of these infections. Given the severe consequences associated with reactivated infection, screening and prophylaxis against hepatitis B is recommended.

Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself, including bone marrow suppression, infection, allergic reactions to rituximab and gastrointestinal toxicity. Social and financial well-being can be impacted by the side-effects of treatment and should also be monitored and addressed.

Overview of regimens

The following provides basic information on administration and dosing for CHOP and R-CHOP; no details are given of ancillary medications pertaining to the management of adverse events. For both CHOP and R-CHOP, six cycles of therapy are recommended.

Standard regimen

- **R-CHOP: chemotherapy plus monoclonal antibody (6 cycles)**
  - rituximab 375 mg/m^2 IV infusion
  - cyclophosphamide 750 mg/m^2 IV infusion
  - doxorubicin 50 mg/m^2 IV injection
  - vincristine 1.4 mg/m^2 IV infusion (cap dose at 2 mg)
  - prednisone 100 mg orally (liquid or tablet)

Alternative regimen

- **CHOP: chemotherapy (6 cycles)**

  - cyclophosphamide 750 mg/m^2 IV infusion
  - doxorubicin 50 mg/m^2 IV injection
  - vincristine 1.4 mg/m^2 IV infusion (cap dose at 2 mg)
  - prednisone 100 mg orally (liquid or tablet)

CHOP or R-CHOP can be given every 21 days without haematopoietic growth factor support. Both regimens can also be given every 14 days with growth factor (G-CSF) support, but the benefit of this shorter regimen is unclear and the additional cost of G-CSF support is substantial.

Review of benefits and harms

Benefits

Given that patients with DLBCL cannot survive without treatment, the benefits of the R-CHOP and CHOP regimens are highly significant. In the GELA LNH-98.5 study, previously untreated patients (60–80 years of age) had improved progression-free survival (PFS) and overall survival (OS) on both chemotherapy and chemotherapy plus rituximab. Addition of rituximab to the regimen significantly improved outcomes: OS at 2 years was 70% for R-CHOP compared with 57% for CHOP *(8)*. A similar study among younger adult patients (18–60 years) produced similar results: event-free survival at 3 years was 59% among patients on CHOP-like chemotherapy and 79% among those on CHOP-like chemotherapy plus rituximab *(9)*. A systematic review by Cheung and colleagues compiled these and other studies to compare outcomes among patients on chemotherapy with those in patients on chemotherapy plus rituximab (R-CHOP) for the treatment of lymphoma *(10)*. As a subset of the larger review, 11 randomized controlled trials (RCTs) concerned with the treatment of DLBCL were analysed. This review is consistent with several other reviews and meta-analyses that have demonstrated the clinically important benefits in terms of PFS and OS among patients on chemotherapy alone or chemotherapy with rituximab *(11-13)*. The difference in OS associated with rituximab shown in the RCT by Coiffier et al., in which two-year survival was recorded in 70% (95% CI: 63–77%) of those receiving R-CHOP and 57% (95% CI: 50–64%) of those receiving CHOP alone *(8)*, has not been replicated in under-privileged settings. In a Mexican retrospective cohort study of patients with DLBCL, OS was 87% at 80 months for those treated with R-CHOP and 84% at 145 months for those treated with CHOP *(14)*. However, the Committee noted the observational nature of the study, the high attrition and the likelihood that those patients who remained in remission at 5 years were cured of their disease and had a high probability of leading normal lives.

Harms and toxicity considerations

Common

The Committee noted that treatment with CHOP and R-CHOP is associated with alopecia and with blood count suppression, particularly neutropenia, which increases the risk of infection. The incidence of grade 3 or 4 infection in patients treated with these regimens is 7–20% *(8, 9, 15, 16)*. Neuropathy from vincristine is rare and usually mild and reversible.

Rituximab can cause significant systemic allergic reactions, neutropenia and, infrequently, viral infection or reactivation of latent viral infection, including viral hepatitis.

Serious

Doxorubicin is associated with a risk of congestive heart failure. This risk is dose-dependent; at the doses delivered in six cycles of CHOP or R-CHOP (300 mg/m^2), the risk is small and was considered by the Committee to be outweighed by the potential benefits of treatment. The risk of long-term bone marrow damage, including secondary malignancies such as myelodysplastic syndrome or acute myeloid leukaemia, is very small (less than 1%). The risk of other secondary malignancies with CHOP and R-CHOP is also small *(9)*.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended that cyclophosphamide, vincristine, doxorubicin and prednisone be specifically endorsed on the Model List for treatment of diffuse large B-cell lymphoma. The Committee also recommended that rituximab be added to the complementary list of the Model List of Essential Medicines for the treatment of DLBCL. In terms of overall survival, the Committee considered that the magnitude of clinical benefit demonstrated by CHOP over no treatment, and by R-CHOP over CHOP (when available and/or affordable), was well established and supported this recommendation. Rituximab should be administered using the standard regimen of every 3 weeks.

The Committee considered that R-CHOP should be the preferred treatment option where possible; where rituximab is unavailable or not affordable, CHOP should be used, since many patients will benefit from this alternative regimen.

The Committee noted that an alternative regimen of R-ACVBP (rituximab, cyclophosphamide, doxorubicin, vindesine, bleomycin and prednisolone) showed overall survival advantage over R-CHOP in a prospective randomized study *(17)*. However, the Committee considered that R-CHOP and CHOP remained the standard of care since this trial might have been flawed, R-ACVBP is not widely accepted, and vindesine is often unavailable.

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