Hodgkin lymphoma (adult) – EML

The application sought the endorsement of medicines already included in the complementary list of Essential Medicines for treatment of Hodgkin lymphoma in adults. The proposed medicines are those in the treatment regimens ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone). The application also sought addition to the core list of granulocyte colony-stimulating factor (G-CSF) for use with the BEACOPP regimen.

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

Introduction

Hodgkin lymphoma is a lymphoid malignancy of B-cell origin occurring more frequently in young people between the ages of 20 and 35 years. It is classified as either nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) or classical Hodgkin lymphoma (cHL) in accordance with the 2008 WHO classification. Although they have characteristics in common, these two disease entities differ in their clinical features and behaviour as well as their cellular properties. cHL accounts for 95% of all Hodgkin lymphomas and can be further subdivided into four histological subtypes: lymphocyte-rich (LR), nodular sclerosis (NS), mixed cellularity (MC), and lymphocyte-depleted (LD) *(1)*.

Hodgkin lymphoma is an uncommon neoplasm with an estimated 65 950 cases globally; incidence varies significantly by age, sex, ethnicity, geographical location and socioeconomic status *(2)* .

Incidence rates are higher in more developed regions and among males and lower in Asia *(3)*. However, Hodgkin lymphoma accounts for 15% of all cancers in young adults globally, with a high impact on quality of life *(3)*. Up to the 1960s, the 5-year survival rate was less than 10% worldwide *(4)*. Since then, the outcome has progressively improved, and the current 5-year overall survival (OS) rate has reached 80% for patients with advanced disease and more than 90% for those with limited-stage disease *(5)*. This success may be attributed to improved chemotherapy and radiation therapy approaches. Among the regimens developed to treat Hodgkin lymphoma, the ABVD regimen is recommended as the standard; the BEACOPP regimen is considered an acceptable alternative for high-risk patients.

Public health relevance

GLOBOCAN estimates for 2012 were 65 950 cases of Hodgkin lymphoma worldwide, with 25 469 deaths *(2)*. Of these cases, 28 852 occurred in more developed regions and 37 098 in less developed regions. The age-standardized rate (ASR) of Hodgkin lymphoma is 2.1 per 100 000 in more developed regions and 0.6 in less developed regions. Regions most affected

by Hodgkin lymphoma include the Americas (ASR 1.5 per 100 000), the eastern Mediterranean region (ASR 1.5 per 100 000), and Europe (ASR 2.0 per 100 000). The highest age-standardized mortality rate, 1.0 per 100 000, is found in the eastern Mediterranean region. Men (ASR 1.1 per 100 000) are slightly more at risk of developing Hodgkin lymphoma than women (ASR 0.7 per 100 000). The disease is most often diagnosed between the ages of 15 and 30 years and in populations older than 55 *(6)*. Risk factors for developing Hodgkin lymphoma include previous exposure to an Epstein–Barr viral infection and infection with immunocompromising conditions such as HIV/AIDS *(6)*.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Pathology laboratory analysis of surgically excised lymph node, lymph node core or extranodal tissue is required. In cHL, the presence of Hodgkin and Reed–Sternberg (HRS) cells is disease-defining, while the detection of lymphocyte-predominant (LP) cells is required for the diagnosis of NLPHL. The immunophenotype of the malignant cells in cHL and NLPHL differs significantly. In contrast to HRS cells, which stain consistently positive for CD30 and CD15, occasionally positive for CD20 and negative for CD45, LP cells are characterized by the expression of CD20 and CD45 but lack CD15 and CD30 *(1)*.

Testing

It has been recommended that pretreatment tests include staging, using contrast-enhanced computerized tomography (CT) scan, and blood counts and blood chemistry to assess critical organ function, including renal and hepatic function, and determine prognosis. Several groups have developed scoring systems to predict survival of patients and guide decisions on therapy. Most consider the presence of constitutional symptoms and bulky mediastinal disease to be unfavourable features in limited-stage disease (stage I/II); stage III/IV disease is considered to be advanced-stage disease *(1)*. Whenever it is available, baseline positron emission tomography (PET) should also be carried out according to the recommendations for staging and response assessment in lymphoma *(7, 8)*. The PET-CT scan can be performed after two cycles of ABVD; complete response is associated with better prognosis and can result in a patient needing fewer cycles of ABVD overall. If a PET-CT is performed, bone marrow biopsy is no longer indicated for Hodgkin lymphoma *(8)*. To identify those at increased risk for acute and/or long-term complications, pulmonary function tests should be performed in older patients. Since chemotherapy and radiotherapy can potentially cause permanent fertility damage, reproductive counselling must be offered to young patients of both sexes before treatment *(9)*.

Administration and care of patients

Administration requires intravenous infusion capacity and regular patient access to clinical care. A central venous catheter such as a Hickman or PICC (peripherally inserted central catheter) aids in minimizing the pain associated with peripheral administration of ABVD. 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 ABVD. Careful monitoring is mandatory to prevent soft tissue extravasation, which can cause severe local reactions and necrosis, especially with dacarbazine.

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, mucositis, nausea and vomiting *(10)*. Special attention is needed for acute reactions to bleomycin, including fever, and anaphylactoid reactions *(10)*. Bleomycin-induced pulmonary toxicity (BPT) may occur in 20–30% of patients, while on therapy or up to 6 months after treatment; patients should be carefully assessed for signs and symptoms of BPT before each bleomycin dose. A history of new or worsening dyspnoea or pulmonary crackles should lead to bleomycin being stopped until an alternative cause is identified *(9)*. Among patients who develop BPT, omission of bleomycin does not compromise the efficacy of therapy, but a diagnosis of BPT itself could potentially compromise outcomes *(11)*. Clinicians should be sensitive to aspects of fatigue and related (emotional) symptoms in their patients and encourage them to seek further support if needed *(12)*.

Overview of regimens

Management of Hodgkin lymphoma (both cHL and NLPHL) relies on multimodality treatment with standard chemotherapy, radiation therapy, and autologous or allogeneic stem cell transplantation in cases of relapsed disease (20–30% of advanced cases) *(13)*.

In many countries ABVD is considered to be the standard of care for Hodgkin lymphoma. Over the past decade, however, other regimens have been developed for patients with advanced (stage III/IV) disease, to improve efficacy or reduce toxicity *(13)*. Dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP), was developed by the German Hodgkin Study Group (GHSG) to improve efficacy; it has emerged as a very effective regimen.

The following provides information on administration and dosing for ABVD and BEACOPP; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimen (ABVD) (14)

ABVD: 2–4 cycles for limited disease, 6–8 cycles for advanced disease (repeated every 28 days)

- doxorubicin 25 mg/m^2 IV infusion on days 1 and 15
- bleomycin 10 000 IU/m^2 IV infusion on days 1 and 15
- vinblastine 6 mg/m^2 IV infusion on days 1 and 15
- dacarbazine 375 mg/m^2 IV infusion on days 1 and 15

Alternative regimen (dose-escalated BEACOPP) (15)

Dose-escalated BEACOPP: 6–8 cycles (repeated every 21 days)

- bleomycin 10 000 IU/m^2 IV infusion on day 8
- etoposide 200 mg/m^2 IV infusion on days 1–3
- doxorubicin 35 mg/m^2 IV infusion on day1
- cyclophosphamide 1250 mg/m^2 IV infusion on day1
- vincristine 1.4 mg/m^2 (max 2 mg) IV infusion on day 8
- procarbazine 100 mg/m^2 orally on days 1–7
- prednisone 40 mg/m^2 orally on days 1-14–
- G-CSF subcutaneous injection starting on day 8

Review of benefits and harms

Benefits

Chemotherapy has transformed Hodgkin lymphoma from a disease that was uniformly fatal a few decades ago to a largely curable disease nowadays. The study by Canellos and colleagues established ABVD as more efficient and less toxic than other combinations *(14)*. In 1992, the Cancer and Leukemia Group B (CALGB) reported the results of a prospective three-group randomized trial involving 359 patients with Hodgkin lymphoma. This trial compared the following regimens: ABVD for 6–8 months; mechlorethamine, vincristine, procarbazine and prednisone (MOPP) for 6–8 months; and MOPP alternating with ABVD for 12 months. The trial was limited to patients with advanced disease (clinical stages III and IV). No radiotherapy was administered. The results indicated an event-free survival (EFS) advantage of ABVD over MOPP but no differences in OS between the ABVD and MOPP groups. However, the toxicity profile was remarkably better with ABVD. These findings were confirmed in a follow-up study of the data published in 2002, and later at a median follow-up of 20 years *(16)*.

Most patients (more than 90–95%) with limited-stage disease, usually defined as non-bulky (largest tumour diameter <10 cm) stage IA or IIA disease, can be cured with 2–4 cycles of ABVD followed by involved-field radiation therapy (IFRT) *(17)*. GHSG recently reported results for their four-group trial (HD13) in which 1502 patients with early-stage favourable-

risk Hodgkin lymphoma were randomly assigned to two cycles of either standard ABVD chemotherapy or one of three experimental treatments, omitting either dacarbazine (ABV) or bleomycin (AVD) or both, all followed by 30-Gy IFRT *(18)*. GHSG aimed to investigate whether omission of one or both of dacarbazine and bleomycin reduced the efficacy of this regimen in the treatment of Hodgkin lymphoma. With respect to the predefined non-inferiority margin, neither dacarbazine nor bleomycin could be omitted from ABVD without a substantial loss of efficacy. The standard of care for patients with early-stage favourable Hodgkin lymphoma should remain ABVD followed by IFRT.

An alternative to ABVD as the standard of care for patients with advanced Hodgkin lymphoma is the intensive BEACOPP regimen, which has shown superior activity to ABVD in terms of improving EFS and OS. However, it is associated with significant short- and long-term toxic effects. Moreover, given the direct medical costs of inpatient stays, chemotherapy drugs and G-CSF, dose-escalated BEACOPP therapy is more expensive than ABVD. Nevertheless, the incremental cost–effectiveness ratio with respect to the absolute gain in OS appears to be favourable *(19)*.

The absolute majority of patients with Hodgkin lymphoma are cured with ABVD. A meta-analysis of five randomized trials examining the efficacy of BEACOPP compared with ABVD for first-line treatment of Hodgkin lymphoma demonstrated the positive impact of BEACOPP on EFS but not OS *(20)*.

A subsequent network meta-analysis identified 14 trials comparing various BEACOPP regimens with ABVD-based regimens in 10 042 patients and demonstrated 7% OS advantage over 5 years, strongly supports the use of six cycles of dose-escalated BEACOPP or eight cycles of BEACOPP-14 (baseline-dose BEACOPP, repeated every 14 days) as initial treatment for patients with advanced-stage Hodgkin lymphoma *(21).* Random-effects meta-regression of absolute OS rates estimated a 5-year OS rate of 88% (95% CI: 84–91%) for ABVD. An additional 7% (95% credibility interval (CrI): 3–10%) benefit was estimated for 5-year OS for dose-escalated BEACOPP, and a 7% (95% CrI: 2–9%) benefit for BEACOPP-14, resulting in 95% 5-year overall survival for both BEACOPP regimens.

European Society for Medical Oncology clinical practice guidelines endorse ABVD as standard regimen for patients with all stages of Hodgkin lymphoma, especially fit patients over 60 years of age. For advanced stages, they emphasize the need for appropriate supportive care and close surveillance if BEACOPP is used, to control short- and long-term toxicities *(1)*.

A similar recommendation was made by the British Committee for Standards in Haematology, the Italian Society of Haematology and the Italian Society of Experimental Haematology, and the Spanish Society of Haematology *(9, 22, 23)*.

Harms and toxicity considerations

Common

Patients receiving chemotherapy for Hodgkin lymphoma will suffer from temporary alopecia and myelosuppression, including suppression of the neutrophil count, increasing the risk of infection (although infection incidence remains low at 2%). The dose-escalated BEACOPP regimen caused more haematological toxicities and infections than ABVD, with subsequently higher risk for transplant-related mortality, especially among those with poor performance status and patients older than 60 years *(20, 21)*.

Serious

Patients should be monitored for symptoms indicating the existence of long-term toxicity, particularly of heart and lung. Treatment with bleomycin may result in late BPT, particularly when combined with mediastinal irradiation. Toxicity may occur in up to 20–30% of patients and fatal pulmonary complications have occurred *(11, 14, 24)*. There may be a significant decline in median forced vital capacity and diffusing capacity *(25)*. A high index of suspicion is therefore warranted, to allow omission of bleomycin as early as possible when toxicity occurs.

Doxorubicin can lead to long-term cardiomyopathy when cumulative doses exceed 450 mg/m^2. However, ABVD provides cumulative doxorubicin doses of 300–400 mg/m^2 and therefore is uncommonly associated with cardiomyopathy.

Escalated BEACOPP regimens are associated with higher risk for gonadal toxicity, especially among women *(26, 27)*. Additionally, the BEACOPP regimen can lead to secondary malignancy in 0–2% of patients, including acute leukaemia and myelodysplasia *(28, 29)*. The ABVD regimen may have lower leukaemogenicity than BEACOPP. Finally, with respect to fatal toxicity, acute treatment-related mortality (TRM) is a matter of concern with BEACOPP *(30)*. TRM occurred in about 2% of patients in the BEACOPP group in the GHSG HD9 trial, caused mainly (87.5%) by neutropenic infections *(31)*.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee endorsed the inclusion on the complementary list of the Essential Medicines List of medicines in the ABVD regimen for treatment of Hodgkin lymphoma in adult patients – doxorubicin, bleomycin, vinblastine and dacarbazine. The Committee did not endorse inclusion in the EML of medicines used in the BEACOPP regimen for this indication, noting that while there was comparable survival associated with the BEACOPP and ABVD regimens, BEACOPP was associated with greater toxicities, including infertility, myelosuppression and secondary malignancies.

The Committee recognized that the procarbazine currently on the list has no indication and could be considered for future deletion.

Further, as empirical use of G-CSF has not been shown to be necessary during treatment with ABVD, the Committee did not recommend the addition of G-CSF to the EML for this indication.

Hodgkin lymphoma (paediatric) – EMLc

The application sought the addition of vincristine, doxorubicin, cyclophosphamide, prednisone, etoposide, bleomycin and dacarbazine to the core list of Essential Medicines for Children (EMLc) for the treatment of Hodgkin lymphoma in paediatric patients. The Committee noted that vincristine, doxorubicin and cyclophosphamide are currently included on the complementary list of the EMLc for other indications.

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

Introduction

Hodgkin lymphoma (HL) is the most common malignancy among adolescents aged 15–19 years *(32)*. It is one of the most curable forms of cancer in young people, with estimated 5-year survival rates exceeding 98%, yet long-term overall survival declines primarily as a result of the delayed effects of therapy *(33)*. Various strategies have been developed – often quite different from those used for adults with HL – that aim to identify the optimal balance between maintaining overall survival and avoiding the long-term consequences of therapy. The regimens described here apply to children, adolescents and young adults, without specific age categories. Chemotherapeutic strategies include combinations of vincristine, doxorubicin, cyclophosphamide and prednisone, and variations that incorporate bleomycin, etoposide, and dacarbazine across North America and western Europe *(34-43)*. Assignment of radiotherapy on the basis of early response to chemotherapy has become a standard across the different treatment approaches.

For standard-risk patients, the application proposed AVPC: (including doxorubicin, vincristine, prednisone, cyclophosphamide) or OEPA: (including vincristine, etoposide, prednisone, doxorubicin). For patients with intermediate- or high-risk disease, the application proposed ABVE-PC (including doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide), or OEPA/COPDac (including vincristine, etoposide, prednisone, cyclophosphamide, doxorubicin, dacarbazine).

Public health relevance

Hodgkin lymphoma is diagnosed in approximately 1100 children and adolescents under the age of 20 years in the USA each year, accounting for 6% of overall childhood cancer diagnoses. The disease ranks as the most common malignancy among adolescents aged 15–19 years *(32)*. In developing countries, there is an early peak before adolescence *(44)*. There is a strong male predominance among children younger than 5 years, while the male-to-female ratio is more balanced in children aged 15–19 years *(45)*. A family history of Hodgkin lymphoma in a sibling or a parent is associated with an increased risk of this disease *(46)*.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Pathological laboratory analysis of surgically excised lymph node, lymph node core or extranodal tissue is required. In classical HL (cHL), the presence of Hodgkin and Reed–Sternberg (HRS) cells is disease-defining; the detection of lymphocyte-predominant (LP) cells is required for the diagnosis of the more uncommon type of HL – nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). The immunophenotype of the malignant cells in cHL and NLPHL differs significantly. In contrast to HRS cells, which stain consistently positive for CD30 and CD15, occasionally positive for CD20 and negative for CD45, LP cells are characterized by the expression of CD20 and CD45 but lack CD15 and CD30 *(1)*.

Testing

Physical examination and diagnostic imaging evaluations (upright posteroanterior and lateral thoracic radiographs; computerized tomography (CT) scans of the neck, chest, abdomen and pelvis, with intravenous and oral contrast; and functional nuclear imaging studies with fludeoxyglucose positron emission tomography (FDG-PET)) are used to designate a clinical stage. Data from retrospective studies suggest that FDG-PET may replace the need for bone marrow biopsies in patients with clinical stage III–IV disease or B symptoms (fever, night sweats, weight loss) *(47)*, but this has not been validated prospectively. Staging laparotomy is rarely appropriate with the imaging modalities currently available, but biopsy of specific sites with equivocal findings by clinical staging should be considered when results will alter therapy. Interim assessment of response by FDG-PET is incorporated into contemporary treatment approaches. However, the optimum time point for assessment and the criteria for response have not been defined. Continued FDG-PET surveillance for relapse within the post-treatment period is not recommended, because of its low positive predictive value.

Administration and care of patients

Chemotherapy for HL consists of multiple agents given intravenously and orally. This requires careful management of fluid and electrolyte balance as well as prophylactic antiemetic therapy and other supportive care measures. IV administration is usually accomplished through a central venous catheter and so should be undertaken only in a specialized cancer centre. Radiotherapy also requires special expertise to minimize exposure of normal tissue.

In the short term, the side-effects of chemotherapy include nausea, vomiting, mucositis, pancytopenia and peripheral neuropathy. In the long term, survivors are at risk for infertility (notably from cyclophosphamide or procarbazine), cardiomyopathy (especially from doxorubicin and radiotherapy), restrictive pneumonitis (especially from bleomycin and radiotherapy), hypothyroidism (from radiotherapy) and second cancers (particularly leukaemia from etoposide and solid tumours in the radiation fields).

Overview of regimens

The following includes basic information on administration and dosing for the Children's Oncology Group and European Consortium regimens; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimens for standard-risk patients

- **AVPC (COG AHOD03P1): three 21-day cycles** *(43)*
  - doxorubicin 50 mg/m² IV infusion
  - vincristine 1.4 mg/m² (max. 2.8 mg) IV push
  - prednisone 20 mg/m² orally twice daily on days 1–7
  - cyclophosphamide 800 mg/m² IV infusion

or

- **OEPA (GPOH 2002): two 28-day cycles** *(37)*
  - vincristine 1.5 mg/m² (max. 2 mg) IV push on days 1, 8 and 15
  - etoposide 125 mg/m² IV infusion on days 2–6
  - prednisone 30 mg/m² orally twice daily on days 1–15
  - doxorubicin 40 mg/m² IV infusion on days 1 and 15

Standard regimens for intermediate- or high-risk patients

- **ABVE-PC (COG AHOD0031** *(34)***; P9425** *(40)***: four (intermediate risk) or five (high risk) 21-day cycles**
  - doxorubicin 25 mg/m² IV infusion on days 1 and 2
  - bleomycin IV infusion 5 units/m² on day 1, 10 units/m² on day 8
  - vincristine 1.4 mg/m² (max. 2.8 mg) IV push on days 1 and 8
  - etoposide 125 mg/m² IV infusion on days 1–3
  - prednisone 20 mg/m² orally twice daily on days 1–7
  - cyclophosphamide 800 mg/m² IV infusion on day 1

or

- **OEPA/COPDac (GPOH 2002** *(37)***)**

  Two 28-day cycles:
  - vincristine 1.5 mg/m² (max. 2 mg) IV push on days 1, 8 and 15
  - etoposide 125 mg/m² IV infusion on days 2–6
  - prednisone 30 mg/m² orally twice daily on days 1–15
  - doxorubicin 40 mg/m² IV infusion on days 1 and 15

  Two (intermediate risk) or four (high risk) 28-day cycles:
  - cyclophosphamide 500 mg/m² IV infusion on days 1 and 8
  - vincristine 1.5 mg/m² (max. 2 mg) IV push on days 1 and 8
  - prednisone 40 mg/m² orally on days 1–15
  - dacarbazine 250 mg/m² IV infusion on days 1–3

Review of benefits and harms

Survival benefits

Special consideration is given to treatment of paediatric patients with HL in relation to the late effects of high cumulative doses of chemotherapy and high doses of irradiation: increased risk of second malignancies and risk of infertility and cardiomyopathy. Paediatric regimens for HL reduce dose and volume of radiation and reduce exposure to anthracyclines and alkylating agents compared with adult regimens.

Radiotherapy usage varies considerably. The Children's Oncology Group recently reported that radiotherapy may be safely omitted in intermediate-risk patients in whom CT scans reveal a rapid reduction in tumour dimensions after two cycles of chemotherapy *(34)*. The European Consortium has omitted radiotherapy for low-risk patients achieving a complete remission after two cycles of OEPA *(37)*. In general, paediatric radiotherapy approaches use lower doses (15–25 Gy) and smaller fields (involved-field or nodes) than adult radiotherapy.

For treatment of cHL, the application identified numerous trials that have used different chemotherapy regimens of varying dose intensity and that have significantly different criteria for omission of radiotherapy.

The GPOH-HD-2002 study investigated OEPA (vincristine, etoposide, prednisone, doxorubicin) for treatment of low-risk patients, and OEPA with COPDac (cyclophosphamide, vincristine, prednisone, dacarbazine) for treatment of intermediate- and high-risk patient groups *(37)*. This study enrolled 573 paediatric patients who received two courses of either OEPA (boys) or OPPA (vincristine, procarbazine, prednisone and doxorubicin) (girls) as induction therapy. Patients with intermediate-stage (TG-2) and advanced-stage (TG-3) disease received a further two or four cycles of COPP (cyclophosphamide, vincristine, procarbazine and prednisone) (girls) or COPDac (boys) respectively. With the exception of patients with early-stage (TG-1) disease in complete remission following chemotherapy, all patients received involved-field radiation after induction chemotherapy.

After 5 years, the overall survival (OS) rate (± standard error) was 97.4% (± 0.7%) and the event-free survival (EFS) rate was 89.0% (± 1.4%) *(37)*. In TG-1, overall EFS was 92.0% ± 2.0%. In patients who received no irradiation EFS (93.2% ± 3.3%) was similar to that in irradiated patients (91.7% ± 2.5%). In TG-2 and TG-3, EFS did not differ significantly between boys and girls (90.2% ± 2.3 vs 84.7% ± 2.7, respectively; $P = 0.12$).

Similar results were observed in the GPOH-HD-95 study of 1018 children and adolescents with HL *(48)*. In this study, TG-1 disease was treated with two cycles of OPPA (girls) or OEPA (boys); TG-2 and TG-3 disease was treated with two cycles of OPPA or OEPA followed by an additional two or four cycles of COPP, for TG-2 and TG-3 stage disease respectively. Patients achieving complete remission did not receive radiation; all other patients received local radiotherapy to the initially involved sites, with the dose depending on the tumour response. After 5 years, the probability of EFS was 0.88 and the

probability of OS was 0.97. There was no difference in the probability of disease-free survival between irradiated and non-irradiated TG-1 patients (0.97 vs 0.94). In the other treatment groups, disease-free survival was significantly worse for non-irradiated patients than for those who received radiation.

The Children's Oncology Group protocol AHOD0431 investigated the rate of induction of complete response after three cycles of AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide) in a single-arm study of 287 subjects aged 21 years or less with newly diagnosed low-risk HL *(35).* At 2 years, EFS was 84% and OS was 100%. Similar results were observed in a prospective trial of 180 patients with lymphocyte predominant HL (LPHL) *(43)*. Of the 137 patients who received three cycles of AVPC, 4-year EFS was 86.6%; OS at 4 years for the entire cohort was 100%. Surgery alone could be considered for completely resected stage I LPHL.

The benefit of early chemotherapy was demonstrated in AHOD0031 a large randomized phase III study that evaluated the role of early chemotherapy response in tailoring subsequent therapy in 1712 paediatric patients with intermediate-risk HL *(34)*. Response following two cycles of ABVE-PC was evaluated. Rapid early responders received two additional cycles of the same chemotherapy, followed by evaluation for complete response. Patients achieving a complete response were then randomly assigned to radiation or no additional therapy. All patients achieving less than a complete response received radiation. Slow early responders received two additional cycles of ABVE-PC with or without two cycles of DECA (dexamethasone, etoposide, cisplatin and cytarabine), followed by radiation. Four-year EFS and OS were 85% and 97.8%, respectively. Among slow early responders, EFS and OS for those receiving DECA were similar to those in patients who did not receive DECA (OS: DECA 96.5% (95% CI: 91.7–98.5%); non-DECA 94.3% (95% CI: 88.9–97.1%; P = 0.16). This trial demonstrated that early response assessment supported chemotherapeutic titration, augmenting chemotherapy in selected slow early responders with PET-positive disease.

Radiation can probably be restricted to those patients with a less than complete response after three cycles of chemotherapy. This approach eliminates the requirement for radiation for more than 90% of patients.

For intermediate- and high-risk disease, the Children's Oncology Group has primarily evaluated ABVE-PC and its derivatives across the risk groups *(40, 41, 43)*. In the P9425 study *(40)*, 216 patients aged less than 22 years with intermediate- or high-risk HL were given ABVE-PC every 21 days for three cycles. Rapid early responders received radiation therapy, while slow early responders received an additional two cycles of ABVE-PC and then radiation. Five-year EFS was 86% for rapid early responders and 83% for slow early responders. Five-year OS was 95%. In the P9426 study, patients received two cycles of chemotherapy consisting of doxorubicin, bleomycin, vincristine, and etoposide *(41)*. Rapid early responders received radiation therapy, while patients with partial response or stable disease received two more cycles of chemotherapy and radiation therapy. Rapid-responding

patients had the same outcome as slower-responding patients despite receiving half as much chemotherapy.

The efficacy of AV-PC (doxorubicin, vincristine, prednisone, cyclophosphamide) was also studied in low-risk NLPHL *(43)*. Patients were treated with limited (three cycles) chemotherapy and those with less than complete response also received radiation therapy. Four-year EFS for the entire cohort of 180 patients was 86.2% and the OS 100%. Again, the majority of patients could avoid radiotherapy, limiting salvage therapy to the few relapsing cases.

The overall 5-year relative survival for 2002–2008 from the SEER database was 84.7%. Children and adolescents have significantly better HL-specific survival than adults (5-year survival rate 96% ± 0.4% vs. 88% ± 0.3%, $P < 0.001$) *(33)*.

Harms and toxicity considerations

Common

Paediatric patients receiving combination chemotherapy for HL will experience significant haematotoxicity, including severe neutropenia – increasing the risk of infection – and high incidences of anaemia and thrombocytopenia. The incidence of serious infection, including sepsis, is relatively high, occurring in 8–17% of patients *(34, 40)*. Many patients also experience stomatitis and mucositis from combined therapy.

Vincristine commonly causes neurotoxicity, including sensory and motor neuropathies, which is typically dose-related. Neurotoxicity is usually reversible and in the regimens described above is typically mild. A small percentage (up to 2%) of patients experience hypersensitivity reactions to intravenous etoposide, which may include angioedema, bronchospasm and/or chest discomfort *(49)*.

Serious

Patients should be monitored for symptoms that indicate the existence of long-term toxicity, particularly of heart and lung, as well as secondary malignancy. Treatment with bleomycin may result in late bleomycin-related pulmonary toxicity; a high index of suspicion is therefore warranted, to allow omission of this drug as early as possible when toxicity occurs.

Doxorubicin is associated with a risk of cardiotoxicity. Development of severe heart failure is uncommon, but myocardial dysfunction may appear in long-term follow-up. In paediatric patients, the risk of heart failure and pericardial disease increases with cumulative doses ≥250 mg/m^2 *(50)*.

Survivors are also at risk of secondary malignancy, associated most commonly with etoposide and dacarbazine in the regimens described above. Although the risk remains small (<3% in the paediatric HL trials listed), patients should be closely monitored for this development *(34, 40)*. Survivors are also at risk for infertility, most notably from cyclophosphamide.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended the addition of vincristine, doxorubicin, cyclophosphamide, prednisolone, etoposide, bleomycin and dacarbazine to the complementary list of the EMLc for the treatment of paediatric patients with Hodgkin lymphoma.

The Committee noted that regimens using these medicines are highly effective but also considered that the alternative regimen of ABVD (considered by the Committee and recommended for EML inclusion in adult patients) is also effective in paediatric patients, and may be more suitable for use in developing countries where therapies of shorter duration may be beneficial and where facilities for management of acute toxicities may be less readily available. The Committee therefore also endorsed the inclusion in the EMLc of vinblastine for the indication of Hodgkin lymphoma.

The Committee also considered it appropriate to include these medicines in the adult EML for HL for the treatment of adolescents over 12 years because the evidence supporting use of these regimens is from trials that included patients up to 21 years of age. This requires endorsement of vincristine, cyclophosphamide, etoposide and prednisolone for this condition on the EML.

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