

*Paediatric cancers: Burkitt lymphoma, acute lymphocytic leukaemia (ALL), Wilms tumour – EMLc*

The Union for International Cancer Control task team on essential medicines requested the Expert Committee to reconsider the cancer drugs listed in the current Model List of Essential Medicines for Children (EMLc).

In 2007, when the first WHO EMLc was published, the list of cancer medicines was modelled directly on those that had been included for adults. In 2011 an application was submitted to divide the EMLc by cancer type instead of by individual drug. The three diseases included were: acute lymphoblastic leukaemia (ALL), Wilms tumour and Burkitt lymphoma (1). The applicants requested inclusion on the EMLc of several medicines that were not incorporated. Thus, in this current application, the Expert Committee was requested to reconsider the following two specific items: medicines for Wilms tumour and medicines for ALL and Burkitt lymphoma.

**Medicines for Wilms tumour**

In 2011, applicants called for the standard regimen for Wilms tumour to be adopted. This regimen included the essential drugs dactinomycin, doxorubicin and vincristine, as well as several others. When the subsequent edition of the EMLc was published, the medicines listed under Wilms tumour were listed as dactinomycin, *daunorubicin* and vincristine. Daunorubicin is not therapeutic in Wilms tumour patients and is not part of treatment protocols. This was not corrected when the next List was published in 2013, and daunorubicin remained. Doxorubicin is listed in the EMLc for both ALL and Burkitt lymphoma; it would not be a new addition. The application requested a change to the original 2011 recommendation, with daunorubicin being replaced by doxorubicin.

The Expert Committee considered that the inclusion of daunorubicin instead of doxorubicin on the EMLc in 2011 was probably a clerical error which should therefore be corrected. The Committee agreed that daunorubicin is not therapeutic for treatment of Wilms tumour and should not be included on the EMLc for this indication. For the treatment of Wilms tumour, the Committee recommended that the medicines included on the EMLc should be dactinomycin, doxorubicin and vincristine.

**Medicines for ALL and Burkitt lymphoma**

In 2011, applicants also called for etoposide to be included in the regimens for ALL and Burkitt lymphoma. Given that the clinical context of treatment remains the same since the 2011 recommendation, the application requested inclusion of etoposide be reconsidered as well. It was noted that etoposide is included already in the Essential Medicine List for adults and is approved for use in children.

### *Acute lymphocytic leukaemia*

In 2011, the Committee considered, and agreed to adopt, a stepwise approach to essential medicine requirements, allowing increasing treatment requirements as experience of management of patients with increasing risk factors is progressively acquired. A five-step approach was recommended:

Step 1: A common protocol for all patients

Step 2: Additional drugs for high-risk patients

Step 3: Dose intensification and need for alternative forms of medicine in steps 1 and 2

Step 4: Medicines requiring intensive monitoring and supportive treatment to ensure safe use

Step 5: The full range of treatment options, including transplant where appropriate (1).

The 2011 Committee considered that medicines listed in steps 1 and 2 should be on the complementary list of the EMLc. These medicines included: prednisolone, methylprednisolone, dexamethasone, vincristine, asparaginase, methotrexate, mercaptopurine (step 1); and doxorubicin, daunorubicin, cyclophosphamide, cytosine arabinoside (cytarabine), hydrocortisone, methotrexate at doses not requiring “rescue” and tioguanine (step 2). These medicines are currently included on the EMLc for treatment of ALL. Etoposide was classified as a step 5 medicine and was not included.

The current Committee noted that, since that review, therapy for children with ALL has continued to advance, and management of these children has become increasingly standardized as paediatric oncologists around the world have become more familiar with successful regimens. Moreover, the toxicities of treatment and necessary supportive care have become familiar to oncologists. Etoposide has been a component medicine in regimens for children with ALL with higher risk features and has contributed to the improving outcome for such children. The incorporation of this medicine has not resulted in a substantial change in the overall toxicity of the regimens.

The Committee agreed that children with ALL with higher risk features should now be offered the more intensive regimens that have been shown to improve outcome. Such regimens include etoposide in addition to the medicines listed above. The Committee recognized that etoposide was an appropriate medicine for treatment of children with high-risk ALL and should now be classified as a step 2 medicine and included in the EMLc for treatment of ALL.

### *Burkitt lymphoma*

In 2011, the Committee noted that the three core medicines for treatment of Burkitt lymphoma were cyclophosphamide, methotrexate and vincristine. Addition of prednisone, escalation of doses of methotrexate, and dose intensity had beneficial effects. Intensive protocols aimed at B-cell non-Hodgkin lymphoma and B-cell ALL, including etoposide, doxorubicin and cytarabine, had led to 90% event-free survival in developed countries, and these protocols have been adapted to low-income countries. The 2011 Committee accepted that treatment typically includes three phases: induction (using cyclophosphamide, prednisone and vincristine); intensive chemotherapy after induction (using the above with doxorubicin, and methotrexate with leucovorin rescue); and consolidation (using cytarabine and methotrexate, and cytarabine with etoposide). The 2011 Committee concluded that all the above-mentioned medicines should be included in the complementary list of the EMLc.

The current Committee noted that medicines currently included on the EMLc for Burkitt lymphoma are cyclophosphamide, cytarabine, doxorubicin, prednisolone and vincristine. In view of the conclusions reached by the 2011 Committee, the present Committee could see no obvious explanation for methotrexate (and calcium folinate (as rescue)) and etoposide not being included. The Committee recommended that the following medicines should be included on the EMLc for the treatment of Burkitt lymphoma: cyclophosphamide, cytarabine, doxorubicin, prednisolone, vincristine, methotrexate, calcium folinate and etoposide.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2011 (including the 17th WHO Model List of Essential Medicines and the 3rd WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2012. (WHO Technical Report Series, No. 965).