Expert peer review on application for trastuzumab

0. Introduction

There are two proposals which recommend the addition of trastuzumab to EML, one lead by the Union for International Cancer Control (UICC proposal), the other lead by Knowledge Ecology International (KEI proposal).

1. Assessment of efficacy
a. Have all relevant studies on efficacy been included
   Yes  No (if no, please provide reference and information)

b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

There is consensus that the addition of trastuzumab to the treatment regimen for HER2-positive breast cancer (20 to 25% of all breast cancer cases) increases survival by 39%, if the tumor is diagnosed in an early stage, and prolongs disease free survival by months or years, if the tumor is diagnosed in a late stage (data from the UICC proposal). An indispensable prerequisite for the treatment with trastuzumab is the reliable diagnosis of HER2 expression in the tumor of the patient.

c. Please provide any additional relevant information with reference

2. Assessment of safety
a. Have all relevant studies on safety been included
   Yes  No (if no, please provide reference and information)

b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

The major adverse effect of trastuzumab is cardiotoxicity. Therefore, specific investigations have to be performed before and during treatment (left ventricular ejection fraction (LVEF) determination). Other side effects are the usual ones when protein infusions are administered.

c. Please provide any additional relevant information with reference

3. Assessment of cost and availability
a. Have all relevant data on cost provided
   Yes  No (if no, please provide reference and information)

Data on the percentage of early and late diagnoses in different settings are missing.

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

The treatment with trastuzumab is expensive, but there is no cheaper alternative. The cost effectiveness seems to be favorable if early stage HER2-positive tumors are treated. This is less clear for the treatment of late stage tumors. Therefore, the overall cost effectiveness depends on the ratio of early and late diagnoses.
It is worse if the percentage of late diagnoses is high, as it seems to be the case in low income countries (as stated in the UICC proposal).

c. Please provide any additional relevant information with reference

d. Is the product available in several low and middle income countries?

4. Assessment of public health need
a. Please provide the public health need for this product (1-2 sentences)

The burden of breast cancer is high, and there is an urgent need to improve the situation of women with this diagnosis. However, there is no single magic drug; instead a bundle of measures is necessary. Most importantly, the clinical diagnosis has to be made as soon as possible, and health systems should aim to achieve this in the first place. In the next step, the characteristics of the tumor (estrogen dependence, HER2 expression) have to be defined. And then, the adequate therapeutic measures (surgery, drugs) have to be taken. Trastuzumab is one essential element in the therapeutic armory.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

NA

5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences

Availability of reliable tests for HER2 expression, surveillance of cardiotoxicity.

6. Is the proposed product registered by a stringent regulatory authority?
   Yes    No

   EMA, FDA, TGA

7. Any other comments

The KEI proposal expects that the addition of trastuzumab to the EML will lead to the reduction of the high costs for this drug. It makes a comparison with HIV drugs. However, to develop a competitor monoclonal antibody might be difficult as exemplified by pertuzumab which is also targeted against HER2 but is less effective. Also the development of biosimilars is much more difficult than the development of a generic. Whether it is possible to get the same molecule by classical methods of monoclonal antibody selection is not predictable. And to reproduce the trastuzumab molecule by other means raises a lot of regulatory questions. In addition the experience with biosimilars so far does not point to a great reduction in price.

8. What is your recommendation to the committee (please provide the rationale)

If the aim is to reduce breast cancer morbidity and mortality a strategy is needed which comprises early diagnosis, adequate laboratory testing and the availability of a number of drugs. Whether it is helpful to add a single drug to the EML seems to be questionable. It might even be risky as it may divert limited resources to the wrong place. In my opinion, the best approach would be to describe all elements of the strategy against breast cancer. Whether and, if so, how it can be achieved in the context of EML has to be discussed.