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Re: WHO Essential Drugs for Cytotoxics: proposed removal of 2 drugs from the List

Dear Sue,

INCTR is privileged to have a role in assisting WHO to update its Essential Drug List (EDL) for Cytotoxic Drugs (CD). In this letter, I would like to outline the procedure that has been undertaken in reviewing the EDL for CD, and to focus particularly at this time on how the proposals for the removal of two drugs currently included in this list were arrived at.

The first part of the process consisted of an informal survey. The EDL for CD was sent to approximately 100 oncologists, including adult (medical or clinical) and pediatric oncologists and some public health specialists practicing in a variety of countries at various levels of development. Among them were senior representatives of some of the relevant professional societies, particularly the International Society for Pediatric Oncology, the European Society for Medical Oncology, and various other major organizations dealing with cancer (e.g., the International Union Against Cancer, the European School of Oncology, the American Society of Cancer) as well as major cancer institutes, centers or agencies. These oncologists were invited to participate in the process of updating the list, and specifically, to identify drugs that might be considered for removal from the present list (e.g., for reasons of safety, more limited indications or obsolescence in the modern era), and to suggest drugs which might be added (e.g., because of proven efficacy in specific cancers, or as a component of specific regimens that have been shown to be more effective in the treatment of specific cancers since the last update of the EDL for ED). It was made clear that the recommendations should be based on an assessment of comparative effectiveness, safety, public health need and cost. The list was refined on the basis of oncologists who declined to participate, or who made recommendations regarding others who would be in a position to provide opinions. Each respondent was asked to provide supporting comments for their opinions.

It is important to recognize that there are few situations in cancer today in which drugs are used as single agents, and that for most cancers in which chemotherapy has a role there are several drug combinations that are considered as "alternatives." Sometimes, but not always, a choice is made on the basis of the different patterns of toxicities, which may increase or decrease the risk of a given regimen for a particular patient (e.g., with specific co-morbidities). Moreover, the efficacy and toxicity of only a relatively small number of these combinations have been directly compared in carefully performed, sufficiently powered randomized studies. Thus, it would be surprising if opinions within the oncological community were uniform with respect to the constitution of an essential drug list. Given these realities, what was being primarily sought in this process was the identification of drugs in which the majority of respondents were of the same opinion.

A total of 54 responses were received from the oncologists polled. Eight drugs were identified by one or more respondents for consideration for deletion from the EDL and 38 were identified for possible addition to the list. As a second step, the entire group of oncologists was asked to complete a table, rating each of the selected drugs with respect to the strength of opinion for its retention (0), removal (+ to +++), or addition (+ to +++). A

significantly fewer number responded. However, among the 8 drugs considered for possible removal, there was high concordance of opinion in the case of three drugs - levamisole, mechlorethine and azathiaprine. The latter, being listed as an immunosuppressant drug in the EDL, will not be considered further. Of the 12 respondents who rated levamisole, 11 were strongly in favor (+++) of its removal. Similarly, 10 of 12 respondents rated the removal of chlormethine as ++ or +++ and one, as +, giving 11 of 12, again, who felt that chlormethine should be removed from the CDL.

As a final step in the process, the literature was reviewed, primarily by Mark Lodge of the Cochrane Cancer Network, with additional, more informal review by myself, in order to assemble available evidence to support the recommendation to remove levamisole and chlormethine from the EDL for CD. Narrative summaries of the case for removal based on these reviews, as well as the abstracts used in the review of evidence, and many of the conclusions drawn by the investigators who conducted specific studies have been provided separately.

A similar process can be undertaken with respect to the drugs recommended for consideration for addition, but it is worth noting some potential weaknesses of this method, which could have a greater impact on deciding upon the addition of drugs to the list. It is not clear, however, that these weaknesses are entirely surmountable, although, clearly, the solicitation of a opinions from a wider audience of the conclusions drawn using the above process, perhaps supplemented by a more detailed review of the evidence base, would provide considerable additional reassurance of their validity or otherwise.

1. Many of the oncologists may not be familiar with the circumstances that apply in a broad range of developing countries, where the list is primarily used, and many, if not most, specialize in particular cancers (e.g., breast cancer, pediatric cancers, gynaecological cancers etc.). The issue of cost may also be relatively difficult to factor into the decision, since this varies greatly from one country to another and one manufacturer to another (all drugs on the list are now generic). Thus, opinions may be biased to varying degrees. Specialist oncologists may feel much more strongly about drugs relevant to their own area of endeavor, and may tend to overemphasize the numerical importance of cancers in their own practice.

2. The overall response to the review - especially the ranking component - was much lower than had been hoped for. While this may have, in part, been because of the amount of work entailed, the difficulties alluded to in paragraph 1, which many of the correspondents would be aware of, may also have inhibited some from responding.

These and other issues relating to attempting to improve the process of updating the EDL for CD process will doubtless be addressed in the future. Whatever the review process finally decided upon, it might be preferable if it were continuously ongoing and proposals readied in time for the annual decision points. In this respect, half a dozen drugs were ranked highly for consideration for addition to the EDL for CD using the process outlined above and would, presumably, be appropriate drugs to consider for the preparation of more formal proposals.

Sincerely,

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President and Director, INCTR