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EDITORIAL

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Always more "setrons": how many do we need?

The possible abuse of "setrons" in radiation oncology [1] has been recently discussed, not to mention the confusing issues about the use of these excellent agents in the prevention of delayed emesis and in the area of post-anesthesia nausea and vomiting. This journal issue contains several important contributions to the area of cytotoxic drug induced nausea and vomiting. It actually opens with a glimpse at the future by S. M. Grunberg, which addresses several issues, both methodological and new agents, such as the NK-1 receptor antagonists [3]. Several such new agents are presently under development, and in view of the promising results of the initial clinical studies he cites, acute and delayed emesis might be better controlled than with present-day combinations. If such agents could decrease the use of steroids in potentially curative settings, they could be of benefit to the patient, as reasonable doubt about the chronic use of of prednisone (admittedly a different approach from short-term antiemetic usage) has recently been expressed in the setting of adjuvant therapy for breast cancer [6]. Other mechanisms of antiemetic action could also be developed, using our knowledge of peptide YY, a good candidate as a mediator of emesis [9]. One might also want to look at mixed 5-HT3 receptor antagonists/5-HT4 receptor agonists, such as R-zacopride, which is under development at present, and not forget the potential of drugs like metopimazine, as discussed by Herrstedt et al. [4]. It is true, as D. Warr says in his contribution in this issue of *Supportive Care in Cancer*, that a combination of a 5-HT3 receptor antagonist and a corticosteroid should be considered a standard in the prevention of chemotherapy-induced acute nausea and vomiting, while the role of the "setrons" in delayed emesis seems modest [10]. As resources allocated for health-related issues are becoming more and more scarce, it is mandatory to discuss the cost-benefit ratio of the use of many drugs, and certainly one can advocate the use of modern combinations in preventing emesis when a high proportion of patients (what is "high"?) can be expected to vomit if left untreated. Guidelines are needed in the same spirit of those that have already been developed for the use of hemopoietic growth factors; the Multidisciplinary Association for Supportive Care in Cancer (MASCC) will soon issue internationally valid recommendations, as it seems difficult to follow the already existing Canadian ones [7] or the soon to be published American ones. However, one should not forget that the world also uses curative, but highly emetogenic chemotherapies in countries with extremely limited resources. What can be done there? In my eyes, companies should offer the "setrons" at cost in these settings, and in these countries one should not forget that metoclopramide and corticosteroids are an acceptable and effective combination, when properly used, and could still be offered as a first-line preventative combination for most cancer patients. But maybe the cost of "setrons" will be pushed even lower, as the competition in the market becomes even fiercer. In most areas of the world we already have granisetron, ondansetron and tropisetron, with variable commercial names. (When will we have a single commercial name all over the world? When will authorities accept that many travel today?) These agents are uniformly efficacious for the prevention of acute chemotherapy-induced nausea and vomiting. There are no data from properly con-

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trolled randomized studies to suggest a major clinically significant difference in efficacy between these agents, at least when they are used at an adequate dose, as discussed by Perez et al. for granisetron [8] and by Warr for ondansetron [10]. So now we have in this issue a paper about a new "setron," which is being introduced in many countries: dolasetron. The development of this agent from phase I [5] until now makes one wonder, as with ramosetron, azasetron and others, if we really had to devolop another "setron." From the data reported in the paper first authored by the late B. Chevallier, it is evident that dolasetron is an efficacious and well-tolerated agent [2]. There are many other papers about the phase III studies with dolasetron, and a couple are alluded to in D. Warr's review. What do these papers tell us about this agent? Nothing of substance, nothing that might make one decide to change his or her prescribing habits. Where is the advantage of this agent? We cannot find evidence of an advantage in efficacy, in schedule, in formulation, or in side effects. The preclinical studies also did not indicate a major advantage for this agent compared to the other available antiemetics. The reality is that the development of this cousin of MDL 72'222, the first 5-HT3 receptor antagonist to be tested as an antiemetic, has been slower than that of its analogues. Do we then need new "setrons"? Yes, because when highly reputable companies bring new agents of the same class into the market, it tends to stabilize and usually decrease the prices of the compounds. This is at least what happened in many of those markets where granisetron or tropisetron were introduced to compete with one or two other "setrons." We can thus hope that at least this aspect will be favorable for the patient and strongly recommend that "setrons" that are still being developed should be brought to the phase III level only if they have, on top of their 5-HT3 receptor antagonist activity, at least some other advantage, i.e., if they actually inhibit other mechanisms. Let us remember how long one thought that high-dose metoclopramide was a dopamine receptor antagonist until its 5-HT3 receptor antagonist activity was actually understood.

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