Eur J Cancer, Vol. 29A, Suppl. 1, pp. S42–S51, 1993
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Supportive Therapy: Challenges for the '90s—Perspectives in Antiemetic Therapy

M. Tonato, M. Aapro, P. Andrews, M.J. Boyce, A. Del Favero, D. Gandara, R.J. Gralla, S. Grunberg, R. Joss, M.G. Kris, M. Martin and F. Roila

ROUND TABLE: CURRENT INDICATIONS AND FUTURE RESEARCH

Gralla: I'd like to first discuss some basic studies and observations. Does anyone have any comments based on the physiology or mechanisms of emesis? Perhaps the person who raised the most controversy and the most interesting ideas was Dr Andrews.

Question from the floor: I'm referring to the problem of late emesis. In our experience, late emesis is a very common problem. I agree with the opinion that the mechanism of late emesis is different from that of acute emesis and I would ask Dr Andrews if he can suggest a possible mechanism to explain late emesis and particularly late nausea. In many studies late nausea is more difficult to control than late vomiting. I would like your opinion, Dr Andrews, and also that of Dr Gralla.

Andrews: I think that the basis for evidence at the moment is that it's probably not a 5-HT_3 mechanism; I think most people would agree that although 5-HT_3 antagonists may have some effect, it's not a major action. The effect that the 5-HT_3 antagonists have may indicate that there is a residual 5-HT_3 release with time after the original cisplatin challenge. My guess at the mechanism is that there are two things involved. One is that the motility of the gastrointestinal tract is certainly disrupted for an extended period of time after the original cisplatin treatment, not only because of direct effects of the cisplatin on the neurons but also because cisplatin does, as part of it's action, cause damage to the mucosa of the gut. Initially I think it changes many of the gastrointestinal reflexes. The analogy here would be with the aftermath of viral infections.

The second mechanism is also to do with the gut, but this is due more to the breakdown products that are produced as cells are killed. The time-course of the delayed emesis coincides roughly with the time-course of the damage to the gastrointestinal tract which is seen in animal studies. As the cells are broken down, cellular products go into the blood stream and can act on the area postrema to induce emesis, and also there are other toxins which may be released at the same time.

Finally, what also happens with cisplatin and also with radiation which we sometimes tend to forget, is that those particular stimuli cause changes in the permeability of the blood–brain barrier itself. If there are any toxins released into the plasma from the gut, then they are able, under these conditions, to reach parts of the central nervous system which they normally would not reach when the blood–brain barrier is totally intact. So, as you might have expected, the answer is a multiple one. In terms of animal studies, the incidence of delayed emesis to intravenous cisplatin appears to be very low in most animals. Part of the reason is that the doses of cisplatin we have to use in animals to cause emesis are very close to the lethal toxic dose. One animal which does seem to offer some hope, although it doesn't vomit, is the rat. What can be seen in the rat at fairly sensible doses of cisplatin is that there is a gross disturbance of gastrointestinal motility which lasts for 2 or 3 days. What is curious is that even after the animal's food and water intake and gut motility are back to normal, their behaviour remains depressed. We have now monitored animals for 2 weeks which have grossly depressed loco-motor activity not due to conductor velocity changes or to lesions of the nerves in the limbs. So there are CNS actions of cisplatin which outlast some of the peripheral effects and these may have a role.

Gralla: A factor, though, which poses some questions, or that adds to the complexity is the fact that Dr Kris has reported that corticosteroids alone have benefit and corticosteroids plus metoclopramide have an even greater benefit. Does this efficacy study give us any hint as to the mechanism of delayed emesis?

Andrews: I think dexamethasone does give very important clues because it tightens the blood–brain barrier. I think that fits in very much with the idea of platinum or something else getting through to areas where it shouldn't.

Question: Is nausea a necessary step to vomiting or can we consider that there might be two separate mechanisms that eventually need different types of treatment?

Gralla: I think here we have a couple of different questions: (1) Are the agents that we are using today, both the new ones and the older ones, as effective against nausea as they are against vomiting? (2) Does this tell us something about the physiology of nausea, which is really vital and a difficult question to study? Perhaps Dr Roila can answer this question: are our agents, either metoclopramide combinations or 5-HT_3 combinations, as effective against nausea as they are against vomiting?

Roila: I think that nausea and vomiting are two distinct entities of a single phenomenon (the act of vomiting), which in antiemetic trials should be separately evaluated. If we consider the response to antiemetic treatment, we can see that more patients are protected from vomiting than from nausea while some patients who vomit don't have nausea. I think that the two phenomena are clearly distinct.

Edited by R.J. Gralla, F. Roila and M. Tonato.
Correspondence to M. Tonato, Division of Medical Oncology, Policlinico Monteluce, 06100 Perugia, Italy.
Received 30 Jan. 1992; accepted 8 May 1992.

Gralla: But can we effectively treat nausea?
Roila: Antiemetic drugs can effectively control both nausea and vomiting, but in some conditions the antiemetic treatment may better control one of the two entities. For example, we have experienced in female patients treated with cisplatin at doses of over 50 mg/m^2 in that the adding of acupuncture to the antiemetic treatment significantly relieves the incidence of nausea but has no effect on reducing vomiting.
Gralla: So we occasionally do have effective antinausea agents without effective or as effective antiemetics. Let me just ask some of the other panel members. Dr Kris, do you feel that the agents we use are effective antinausea agents in addition to their antiemetic effects?
Kris: Based on the data we have collected using visual analogue scales, which I believe are imperfect but are probably the best instrument for measuring nausea, we found an excellent correlation between the nausea scores and nausea control and vomiting scores and vomiting control with the drugs that we have now.

That answers the two questions: (a) do the drugs work, and I believe that they do for both entities and (b) whether they are separate phenomena or not. Based on those data, I would say that although they may be separate phenomena, their control goes together. In the literature the preponderance of the evidence is that the drugs that effectively control vomiting also effectively control nausea.
Gralla: Dr Joss, I'd like to ask you the same question. I've seen some studies presented with granisetron where there was discussion that the antinausea control was particularly good. Is my recollection of that correct, or do you have a different feeling?
Joss: I certainly agree with Dr Kris, and basically concur, at least in the majority of patients.
Gralla: So there's a consensus that most of the drugs for the majority of patients are reasonably effective against both nausea and vomiting, but there are some patients who are exceptional in both areas. Overall, the effective antiemetics are also effective antinausea agents.
Question from the floor: I suspect that part of the problem is that vomiting is obviously very easy to assess; nausea is much more difficult.
Roila: We have had a large experience in the assessment of nausea in over 800 patients and we've evaluated two different measurements, the score (0 = no nausea, 1 = slight, 2 = moderate, 3 = severe nausea) versus a linear analogue scale and we saw that the two methods of evaluation of nausea have the same reliability. We prefer to use a score because it's easier for the patient. Also, we have analysed three dimensions of nausea. One, the maximal intensity of nausea, the second the entity of nausea which was the sum of nausea referred by the patient in the 24 h of observation and the third dimension was quantity of nausea which was the product of intensity for duration of nausea. We have seen that quantity is more reliable than entity and entity more than maximal intensity of nausea. The quantity of nausea is a more reliable and more sensitive measurement than the other measurements in describing the different incidence of nausea when the patients are treated with two different antiemetic regimens.
Gralla: Thank you very much. Dr. Andrews, do you feel that there is a different physiology involved with nausea and vomiting, and do you feel that 5-HT$_3$ receptors are involved in the physiology of nausea?
Andrews: Nausea and vomiting can be driven by the same stimuli; therefore, if you block the activation of the system then you will block both. So, I think that 5-HT$_3$ antagonists do have a role. I do not think that all the 5-HT$_3$ antagonists are the same as far as nausea is concerned, but the one thing we have to very clearly distinguish is that vomiting and retching are reflexes. If you take a decerebrate animal or even an anaesthetized one, it will vomit and it will retch. It will not clearly experience nausea. But if it has the frontal parts of the brain it responds as if it has nausea, as a behavioral correlate, and we can influence that behavioral correlate. Part of the problem with assessing nausea in patients is what people understand by the term nausea and from my limited experience with this, you have to be extremely careful how you ask the question. For some people, nausea is a gastrointestinal disturbance, it's not the immediate urge to vomit, and all patients may not be describing the same thing. You have to tell them what nausea is and then say, "Do you have this?"
Gralla: Certainly, instrument development is very important. We notice many regional differences with all sorts of expressions being used.
Aapro: I think that with the instruments we use for the assessment of nausea and vomiting, there can be a methodological problem. We have several people at this meeting working on quality of life studies who are looking at the visual analogue scales and the parallelism between them for nausea and vomiting. In those visual analogue scales, generally you have the best result on the left and the worst on the right. There have been studies where it has been shown that people tend to give the same type of answer when the questions are related.
Gralla: In our quality of life and antiemetic studies we had variation among the scales. We also had the scales on different pages to avoid tracking.
Williams: I'd like to add to Dr Roila's comment that acupuncture may have a differential effect. We've just finished a study which used acupressure at the P6 point in the wrist vs. a sham point on the ankle in patients receiving high-dose chemotherapy including cisplatin. We looked at the number of emetic episodes, visual analogue scales, diary recording, etc. and in that study patients who had the active acupressure did better than the patients who had the sham acupressure concerning both nausea and vomiting. It is a suggestion that maybe a totally different mechanism has an effect on both sides.

What I wanted to do was to be provocative to Dr Andrews and say that he's doing a jolly good job. I really did like his talk, but at the end of it I think there were more questions than answers. As empirical clinicians should we not pay any attention to his talk and should we go ahead and empirically put together our combinations and let him answer the questions when we come up with the best combination?
Gralla: I think that Dr Andrews' role here was to ask more questions than to give answers.
Andrews: I think there is a problem with the clinicians' application of pharmacology and this is going to come out very soon with the 5-HT$_3$ antagonists. Every time you talk to somebody, if one study doesn't work they say well, we have another trial planned where we're going to go four times the dose or 10 times. This is not going to work with these agents. You have to understand some of the pharmacology to be able to prescribe the 5-HT$_3$ antagonists because they have very strange dose–response properties. As we saw this morning with the study of the Spanish benzamide, you go very quickly

over the top of the dose curve and they have very narrow active areas, particularly the benzamides. I think that there are other aspects about the pharmacology which are important to understand in terms of the mechanism. We are seeing very potent antiemetic agents, but what this is leading to is clinicians getting hold of these and trying them under all sorts of emetic circumstances then saying, no, this is rubbish, they are not antiemetics. It is important that clinicians understand that these will only work in situations where there is an elevated or changed 5-HT metabolism involving a 5-HT_3 receptor. So, it is only in cytotoxic therapy, radiation, and maybe one or two other rather rare occasions when they will be antiemetic. These agents do not work against motion, they do not work against all types of emesis, so I think in that respect, you do need to understand some of the basic science so as not to make clinical mistakes. As far as all the agents that are available are concerned, they are safe and we know doses and modalities of administration. I think you can put them in any combination that you feel you can get funding for and we may come up with the answer simply because we don't know how all these things work. I go back to the dopamine story, and that is a good clinical example of an accident; there is really no scientific evidence to tell you what on earth is the involvement of dopamine receptors in cytotoxic-induced emesis. There is no data other than if you put haloperidol into somebody it seems to help. I would say that here is where pharmacology becomes important. We use domperidone as a selective D2 antagonist and domperidone clearly has very little effect; you can't use it interchangably with haloperidol because haloperidol has many central actions outside the area postrema which domperidone does not have. This is a very important clue: we ought to understand more about the neuroleptic effects of haloperidol, not purely its D2 effect. I think it has actions other than D2 which contribute to its antiemesis.

Gralla: I'd like in the next few minutes to concentrate on the physiology of emesis again.

Joss: I have a question for the pharmacologist. If we assume that these agents actually block receptors, then one might think that once you've blocked all the receptors, you won't do better with higher doses, and that's probably something we see above a certain dose. For most of the agents, in fact, you don't do better in increasing the dose. There were even some suggestions that you have a bell-shaped curve. The question for Dr Andrews is, do you think it's true that we block a certain amount of receptors, and then that's it, or do you think you can increase the dose and get a better response?

Andrews: When all the receptors are blocked then yes, the response goes. The trouble with many of these agents is that as you increase the dose, you recruit an effect on another receptor. So, you have your 5-HT_3 receptor fully blocked, you increase the dose, and recruit an action on another receptor which looks as if it's not beneficial. This is almost certainly what's happening with the benzamides.

Gralla: But, Dr Andrews, if I could interrupt, that doesn't seem to happen with metoclopramide, even with doses up to 6 mg per kilogram.

Andrews: In some of the benzamides it seems to happen.

Gralla: And aren't we supposed to believe that the 5-HT_3 inhibitors are very specific for 5-HT_3 receptors?

Andrews: They are extremely specific for the 5-HT_3 receptors based on current knowledge and you know, we find anomalies in the dose–response curve; they're normal curves up to a particular level, then they start to fall apart. One of the things we now know, for example, is that ICS 205930 is certainly a very selective 5-HT_3 receptor antagonist, but at higher doses, it's a 5-HT_4 antagonist. That may, if it's true for some of the other compounds, explain why the effect then goes off, because you recruit a disadvantageous effect. It may be that the gut stimulation that some of the agents produce is in fact disadvantageous because it's so potent.

Gralla: So, we are leaving the door open for the fact that these agents may have a major role on a different receptor heretofore untested?

Andrews: In the intestine, yes, and in fact if you look at the clues in the clinical trials, you'll notice that one of the common side-effects is constipation. Some of the compounds do it better than others. If you tease out that effect, you'll find there's another receptor in the colon. I think in the clinical trial design, what you have to do is get as many doses as possible, not just go up four to 10 times in dose. You can be straight outside the range on your first step, so you have to do smaller steps.

Gralla: I would say that, unfortunately, 10 years ago, not all the pharmacologists involved had the same broad view as yourself. In fact, we were told by pharmacologists that there was no sense in increasing the dose of metoclopramide. Fortunately, at that point we followed a careful, gradual dose-escalation scheme.

We see that mainly the laboratory scientists doing animal studies are the ones guilty of the 10-fold increases. In the clinic, increases are not nearly that size. Most of us like to escalate the doses to the point where we see some sort of an effect; either a negative effect or some fall-off in efficacy. And in fact, frequently we are not allowed to do those studies.

Andrews: I think that's right, I think the cautious approach is the best one. Just on this business about blocking all the receptors. One of the things we tend to forget is that the receptors actually turn over. They're not a fixed population and one of the problems is that if you're in a system where there's an afferent with a 5HT-containing cell next to it that's releasing a lot of 5-HT, the receptor turnover is going to be quite different. This may be the only way you can explain how these agents have such long effects on cutaneous flare response, 24 h or longer, which does not predict the duration of antiemetic action. It has to be that the turnover of 5-HT receptors in cutaneous afferents is much, much lower than in the gut afferents.

Grunberg: I would like to make a couple of points concerning the difference in action with haloperidol as compared to some of the 5-HT_3 antagonists. We certainly see that several different substances that serve as antiemetics may not operate through the same pathways. Traditionally we think of the flow of knowledge from basic science as being established in the laboratory and moving into the clinic, but as has been demonstrated by Dr Emil Frei on numerous occasions, I think this may be an excellent example of a place where clinical observations can then be used to challenge a basic scientist. If you do not believe that this (haloperidol's antiemetic activity) is a dopamine effect, then please tell us what it is, so that we can design further combinations. In terms of the question on the saturation of receptors, this is certainly one that has continued to puzzle me, and I think in some ways has unfortunately inhibited the development of some of these agents. We've heard about several being examined at particular doses, what might be called low or moderate doses, that have had antiemetic efficacy, but have certainly not been anywhere near the

maximal doses or even the maximal blocking doses. In our experience as some of these studies developed over the last several years, we were told that we did not need to and should not escalate above these moderate doses because it was obviously enough to block all of the receptors. We have now been analysing some of our pharmacologic data from our phase I study of ondansetron. A point that one must remember is what the adequate dose is depends on how it is defined. If one defines the adequate dose as the one at which a significant number of patients receiving cisplatin, for example, will have no vomiting, one finds that from very low doses of ondansetron all the way up the scale one sees an approximately equivalent number of patients having no vomiting. However, if one looks at the other end of the scale, at the number of patients who have total failure, we found that at the lower dose levels, actually the area under the curve, we did see patients who were total failures. When we got to the higher dose levels, the percentage of patients who had zero vomiting episodes did not change, but the percentage of patients with 4 or 5 vomiting episodes decreased and the maximum number of vomiting episodes went down. This would imply one of two things. One is that either because of lack of access of the drug to receptors or some other cause of intrinsic resistence, that we had not saturated the receptors at the levels or doses at which the animal studies said we should, or that there is indeed another set of unidentified receptors that is not recruited until we get to the higher doses. And once again I'll throw this back to the laboratory to tell us which of these models is correct. I don't think we should just be stuck at these lower doses because there is something else to be learned and something else to be gained at the higher doses.

Andrews: I would very much agree with you and we can certainly look at haloperidol in the ferret. But one problem we have to remember with these drugs is that they are competitive antagonists and, of course, if the amount of 5-HT that's coming out in a particular patient is higher then it will overcome the drug and you need then to boost the dose. At the very high doses of metoclopramide that are used, it's not totally a non-competitive antagonist, but it's getting dangerously close to it in its 5-HT_3 action at high dose. It's slightly non-competitive rather like MDL 72222 is; it's slightly non-competitive at high doses on some of the assays.

Gralla: I'd like to conclude our physiology portion with just a couple of questions for Dr Andrews and then we'll move onto the clinical studies. I'd like to take a somewhat irreverent view towards the 5-HT_3 mechanism. I'm still troubled by the fact that patients who have had a more than ordinary vagotomy, in patients who have had major abdominal surgery such as an oesophago-gastrectomy, tend to have a very high incidence of emesis with high-dose cisplatin, nearly 100%. I'm still troubled, at least in the animal studies, that the application intracerebrally or intraventrically of 5-methyl-HT does not cause emesis. I'm troubled by the fact that patients who have carcinoid syndrome in which they excrete enormous levels of 5-HIAA do not have emesis as part of that very symptomatic syndrome. I agree that 5-HT_3 receptors, or 5-HT_4 for that matter, are important, but I feel that it's not the whole story.

Andrews: I'll try and answer as briefly as possible. First, the carcinoid syndrome. It's always bandied about that patients with the carcinoid don't vomit, but in fact, if you look at some of the original papers, then there is some vomiting. It's not a big percentage, it's not a problem, though, because when they have the carcinoids they have a raised plasma 5-HT level and what will happen is, because the plasma level of 5-HT is raised slowly then you can get tachyphylaxis access of 5-HT on the type 3 receptors very quickly. If you use that Bezold–Jarisch reflex and give multiple 5-HT injections, and if you don't give them more than 15 min apart, you don't get a response or you get a markedly reduced response each time, so 5-HT_3 receptors rapidly desensitise *in vivo* so the carcinoid's not really a problem. I think the animal studies do need a lot more work. All we're saying is that as far as the ferret's concerned, the vagus is important and gives a site of action that may be applicable to man, but I would welcome good vagotomy clinical studies as much as you because it's the only way we're really going to resolve this. I would caution that the emetic reflex is plastic, it does rewire, if you take one part of the pathway out, there's another, and I think we have to be very careful. I'd throw the question back to you: clinically, do you want something that blocks emesis from all causes, because the feeling I'm beginning to get with using these multiple combinations is not just for chemotherapy, but you actually want to get something to block the vomiting center, and I think this is rather worrying, because the vomiting center doesn't exist, really. It's just the way a particular bunch of neurons fire together and if you want an anatomical site for it, it's the nucleus tractus solitarius, and since that controls respiration, the cardiovascular system and most of your autonomic nervous system, if you start playing around with the pharmacology in there, unless you're very careful, there's going to be a lot of problems.

Gralla: I'll take you back 10 to 12 years ago when we were told the same thing, that you could not stop chemotherapy-induced emesis, because you'll stop breathing, and for the majority of patients . . .

Andrews: What I'm saying is chemotherapy is not a problem, it's the specific part . . .

Gralla: We're just talking about chemotherapy here.

Andrews: Yes, fine, chemotherapy's no problem, but central blockade chemotherapy is potentially very bad news because of the side-effects.

Gralla: Fortunately, Dr Roila has told us that he has stopped emesis in 91% of his patients and I trust they weren't all on respirators.

Now, moving on, the next study is by Fausto Roila. Your study is most encouraging, the ondansetron versus ondansetron plus dexamethasone, but I have trouble with the degree of antiemetic efficacy overall. To have 64% complete control of cisplatin-induced emesis with ondansetron alone troubles me; maybe it troubled you. It's nice to be concerned by good results, but it seems to be such a high degree of control for a single agent. It is 50% greater efficacy than seen in many prior studies even though the median dose of cisplatin was less. Can you give us some of the results with the patients getting 100 mg/m^2 of cisplatin, both for ondansetron and ondansetron plus dexamethasone.

Roila: I think that the prognostic factors are important in evaluating the results of each antiemetic trial. In fact, in our trial on ondansetron vs. ondansetron plus dexamethasone, the mean dose of cisplatin was 75 mg/m^2, less than our usual mean doses of cisplatin of 90 mg/m^2 and this can explain the 90% complete protection. I would like to add an observation with respect to the previous discussion. I think that we obtained very impressive results with antiemetic combinations, because to cover 75% of patients from vomiting is an

impressive result. What we need to identify are the causes for which there are subgroups of patients who vomit more than others. For example, why did women have more vomiting than men, why younger more than older. This is another problem which we need to evaluate.

Gralla: But Fausto, I don't want you to get away too easily. Do you have the data of those patients treated with 100 mg/m^2 of cisplatin, just taking that subgroup and looking at the ondansetron vs. ondansetron plus dexamethasone. Could you share those results with us? I think it could be valuable.

Roila: In our trial the patients treated with doses of cisplatin superior to 100 mg/m^2 were few and in our multifactorial analysis we show that one of the important prognostic factors in determining a complete response from vomiting was sex, age and dose of cisplatin. The mean number of vomiting episodes was less in patients treated with lower doses than with higher doses of cisplatin.

Gralla: The reason I bring it up is that we're going to want to try to conclude with an analysis of an overview of the 5-HT_3 analogues. One of the areas we have in common is that of treatment in patients receiving high doses of cisplatin. On the other hand, it may be that certain subgroups may benefit more by one approach more than by others.

Question from the floor: The question is extremely relevant and revealing, as the presentations today have touched upon. One, it is clear in subset analysis, that the response is dependent on the dose of cisplatin used. In Dr Gandara's study, clearly, he threw out the variability of cisplatin dose and dealt with 100 mg/m^2 as the starting point. I believe in Dr Boyce's study, that he dealt with time of infusion. Clearly, the speed with which you give cisplatin determines how much vomiting and how much nausea you get. Few of these studies have dealt with these issues in a critical fashion. We as clinicians are going to have to restrict our variables and study them in subset analysis.

Roila: We infused our cisplatin in 20 min, but there are some experiences published some years ago by Jordan that show that an 8-h infusion of cisplatin reduces the number of emetic episodes with respect to short-time infusion.

Gralla: We've talked about new drug development. Each one of these agents can be shown to be highly effective. If we take the example of high-dose cisplatin, we're talking about an emetic rate of nearly 100%. The literature would support 99%. This emetic rate is no secret; this is something that was published by 1982. Yet there was a study published on ondansetron given to patients receiving cisplatin who were compared with a group receiving placebo (Cubeddu LX, *et al. N Engl J Med* 1990, **322**, 810–816). We've been told about a study with granisetron in which patients were not given any antiemetic to start with. I know that the explanation given was that there would be rescue for the patients later. Well, it's a good thing, because it must have been known that they would need to be rescued. What I'm asking is, have we learned anything clinically from these placebo-controlled studies in the late 1980s that could not have been learned otherwise? Was this valuable enough to ask patients to receive no treatment or placebo, which was certainly doomed to lead them to have what is certainly the most feared side-effect of patients receiving chemotherapy.

Del Favero: I think the point raised by Dr Gralla is very important. The recently published trial by Cubeddu in the *New England Journal of Medicine* to which he referred is not the only example. I think we have to make a consensus statement on these points. I think as researchers we are pressed frequently by the pharmaceutical industry, for the regulatory agencies, to have some sort of placebo-controlled protocol. We must always keep our patients in mind and we have to be very careful to resist this kind of pushing. I think we can fight together against these pressures. But I want to expand the problem to an ethical issue and to two other points, perhaps less important and more questionable, but I think it's important to consider them. The first point is the "me too" drugs. I think we are looking in every field of pharmacology and therapeutics to be requested to do more and more pharmacokinetic studies, dose-finding studies and so on with very similar drugs. When you find a very interesting drug, immediately after perhaps there are more interesting drugs, but most of them, unfortunately, are not as good as the first one. This is losing time, losing money, and what I'm more interested in, it can put the patient at an unacceptable risk of more vomiting and more nausea during drug testing. Can we accept more studies on drugs that have no valid experimental or pharmacological reason to be tested? This is the first ethical issue. The second one concerns changing schedules, doses or the way of infusion, and so on. Is this acceptable?

Gralla: Thank you, well taken. Just getting back to the placebo question, do we have a defender for the placebo studies, who feels that the lesson has been valuable enough to ask our patients to be that altruistic? Dr Grunberg.

Grunberg: Actually Dr Gralla is asking two separate questions and they should be addressed separately. I think most of us, if not all of us, feel very uncomfortable with the idea of a placebo-controlled trial against an agent such as high-dose cisplatin at this point. Personally, I don't see how one could obtain truly informed consent from patients to be in a placebo-controlled trial if informing them means telling them that if they don't go on the study we can certainly give them metoclopramide and dexamethasone with a 60% chance of not vomiting at all. On the other hand, as I looked at the study that was published in the *New England Journal of Medicine* I think the finding in that study that administration of cisplatin causes a marked rapid release of urinary 5-HIAA is potentially a very important finding. If this were true, and if you had just used the ondansetron-alone arm, one might have been able to make the argument that it was merely a response to having received the 5HT_3 blocking agent first. So that if one accepts that this could be an important finding then one would have to find a way to do such a study without confounding it with the other agent.

Gralla: Well, of course Dr Andrews was kind enough to critique that study beforehand and felt that it didn't answer the question, in that emesis itself may cause the release of serotonin. Additionally, I didn't see a reference for it having been done in animal studies first. Would it be reasonable for this group and for this panel to write a letter to the *New England Journal of Medicine* to say that this is not appropriate, and that this should not be part of the development of a drug in the future, especially with cisplatin-induced emesis.

Roila: In March, after the publication of the article of Cubeddu, we sent a letter immediately to the *New England Journal of Medicine*, to say that it was an unethical study and that it is also a problem that this study was accepted by the local ethical committee (Roila F, *et al. J Clin Oncol* 1991, **9**, 891).

Gralla: Moving on to another area, we're looking for differences among these agents. Dr Joss, a factor that may or may not be important with granisetron is the liver tumour problem that apparently has not been seen so far with some of the other 5-HT_3 inhibitors. Do you want to comment on that?

Joss: Yes, what Dr Gralla is alluding to is that in carcinogenic studies lasting over 2 years with a dose which is 100 times more than the dose which is used in clinics, the researchers found liver tumours, adenomas and carcinomas. The question arises whether one should continue to use granisetron in the clinic. I think that what one has to say is that there is a dose where there is no effect and that is 1 mg/kg in animals, a dose which is still above that which we're using in the clinic. And though from my point of view it is ethical to use this drug, I'm not sure that with other drugs carcinogenecity studies at these high doses have been done, 100 times above the clinical dose.

Gralla: Thank you. Dr Andrews, do you have some other information?

Andrews: I think you have to be very careful with this assessment of the toxicity problem. This is daily dosing of what you said, 100 times over a period of 2 or 3 years, so I think individuals can assess how relative that is to normal clinical usage. The second point that I think really does have to be faced is whilst this problem certainly does occur with granisetron and is reported, when you look at the number of times a therapeutic dose was used, it's effectively difficult, if not impossible, to do that number of times the therapeutic dose for the other compounds, because the animals die.

Gralla: The other point is that many carcinogenicity studies are done using extremely high doses and the relevance of such studies can be questioned. Certainly, for our patient population and on our schedules it seems even less relevant, but nonetheless it is a problem.

Andrews: It has to be faced. I wonder, actually, whether metoclopramide, when it came out, you didn't have to do the same regulatory procedures. If somebody now showed that metoclopramide has this effect, would you stop using it? At high doses?

Williams: Just to support what Dr Joss has said, it's not necessary to conduct carcinogenecity studies for registration of an antiemetic.

Gralla: I'd like to move on to the next drug, ICS 205-930, if I could, and I thought that both the information from Dr Williams and Dr Kris was very interesting and that the drug itself appears quite effective. Do we know, Dr Williams or Dr Kris, what the future of this drug is?

Kris: I do not believe that the proper dosage and schedule for this agent has been determined. It's clear that over the range in the study the drug is safe. It does lessen emesis caused by chemotherapy, including cisplatin, but the optimal dose and schedule is not known. Whether the long half-life will translate into therapeutic effect is also not known. To the best of my knowledge, there is no oral phase I trial and I would suggest that this be a separate trial. You cannot extrapolate the data from the intravenous to the oral. Metoclopramide is an example—it has a different spectrum of side-effects when given orally instead of intravenously, in terms of dystonic reactions, for example, and I would encourage the developer of this agent to do a full phase I study with the intravenous and oral drug. For the problem of delayed emesis, it's again another issue that is a difficult one. Whether or not the 5-HT_3 antagonists work in delayed emesis is an interesting question. I think Dr Andrews raised this point. Our data shows that these agents are no different from placebo in delayed emesis following high-dose cisplatin treated scarcely with metoclopramide, dexamethasone, lorezepam.

Gralla: So, Dr Kris, your study then with ondansetron agreed with Dr Gandara's. But, if I recall correctly yours was a comparison with historical controls and you were unable to identify efficacy by giving 8 mg of ondansetron.

Kris: Well, actually I disagree. It was not identical with Dr Gandara's. We had a different incidence of nausea and vomiting on the placebo arm. I think one reason for that was the treatment during the initial phase of the study. The metoclopramide schedule and dose were different; all our patients received dexamethasone also, which clearly would have had some activity in the time we're looking at. But as far as the treatment regimen, I think the one published randomised trial against placebo shows that metoclopramide and dexamethasone can reduce delayed emesis in nearly half the patients, and that's the regimen I'd recommend.

Gralla: Dr Kris, are you doing further studies with ICS 205-930 and are you aware of any studies that are ongoing in the U.S.A. with the ICS 205-930 agent?

Kris: To the best of my knowledge, there are no trials in the United States right now and the ones that were started have been suspended.

Gralla: Dr Williams, with your interesting data, are you aware of any further studies that are ongoing presently?

Williams: I think the current situation is, as I understand it, Sandoz do intend to continue to develop and to market the drug. This conference actually comes at a very opportune time to help plan what study should be done. I think that Dr Kris is right. We need to look at the dose and schedule as a single agent and then to think if we can sort those questions out. How do we put this agent into combination?

Kris: If anyone talks to the Sandoz people, please remind them of the lesson said many times today, of metoclopramide. Careful attention to dose and schedule, and a testing of the hypothesis is what led to its usefulness and to a lot of basic science revelations also. I want to make sure that same situation is not repeated with this drug.

Gralla: The question of dose is particularly important and brings to mind something Dr Boyce brought up during his presentation. Dr Boyce, you mentioned the use of a unit dose, not based on mg/kg or mg/m^2 but a single dose. How do you feel about that? Do you think it's something we should try?

Boyce: Well, I have to say it's a difficult choice to defend, in many ways. Having looked at the existing literature on 5-HT_3 antagonists, our own experience with the 20 mg dose of MDL72222, although my own feeling is that we should look at a mg/kg basis to start with, I was persuaded by colleagues that we ought to keep it as simple as possible. We're looking to use these drugs in routine clinical practice and if the data is available for a rounded out dose, then that makes life simpler for everyone. I have to say that the meeting in London last year in September when the Beecham data on granisetron was presented, the representative from Beecham said that it was likely that the dose would be rounded out at 40 μg/kg. This is about 3 mg for a 70 kg man and that was probably going to be the recommended dose. So I think what often happens in the industry, if you start out with a mg/kg dose you end up rounding out anyway. Ours are preliminary dose-finding studies and if there's anything in it that looks as if it's related to surface area then obviously we will explore it within

a subset analysis and then we'll carry out controlled studies in that way.

Gralla: Thank you. I'd like to move ahead rapidly; Dr Grunberg.

Grunberg: Just in terms of this question of fixed dose, scientifically it seems so much more pure to us to adjust the dose on some basis. In essence, it's a pharmacological question and sometimes we forget what we do every day in other settings. The requirement for a fixed dose is two-fold. First, we need a set of agents that has a therapeutic index that is very wide, and second, we need a set of agents that has a toxicity profile that is very low. None of us has any problem in ordering antibiotics on a fixed dose basis. We don't think twice about it because many of the antibiotics do fit these two requirements. I think the question is not if there is something intrinsicly wrong with ordering these agents on a fixed dose basis or packaging them on a fixed dose basis. The only question is, do the 5-HT_3 antagonists fit these two requirements?

Gralla: Certainly a good question. Dr Gandara.

Gandara: I would add that for ondansetron, the same question has come up, particularly with regard to using a fixed dose and also a single dose, similar to the studies with granisetron. We're currently conducting a randomised trial of the standard dose of ondansetron, 0.15 mg/kg for three doses vs. single fixed doses of 8 mg intravenously or 32 mg intravenously. At least for ondansetron, that should help to determine whether per kg dose is better and also should help to look at the possibility of whether the single dose is as efficacious as repeated doses.

Kris: Just to comment on that, we have already done a trial with ondansetron, giving the same total dose, 0.45 mg/kg as a single intravenous dose and we have found that it has a lower complete response rate than our prior data giving three doses or two doses, and also a lower major response rate.

Gandara: I'd like to ask Dr Kris, is it due to that late breakthrough. Is that where the problem lies in terms of emesis?

Kris: With that, yes. I think that no matter what dosing schedule of ondansetron has been used, even with people getting it every 8 h.

Grunberg: There's another point, before we go too far. If you look at a 0.15 mg/kg dose, it means that for the vast majority of patients you're going to be giving somewhere between 10 mg, three times, and 12 or 13 mg three times. If all the other data points fit the two requirements I mentioned, I'm not sure how much time we really should spend or how many patients we really should devote to seeing if somewhere between 10 and 12 mg three times is any different from a fixed dose that falls right in the middle of this range. I'm just not sure if all these are worthwhile studies for anything except marketing purposes.

Kris: There are reasons to try to give the drugs as a single dose. For patient convenience, staff convenience, and for cost reasons. So, it's not simply the question of trying to give fewer dosages of an agent.

Gralla: We do see patients who weigh 40 kg and we see patients who weigh almost three times that much, and who have at least 50% greater surface area. I think there are two sides to the question. I can see we will not come to consensus on this point. I was asking Dr Aapro a question a few minutes ago. One is, I was struck by the review of the benzamides and I'm a little confused as to what to do with some of them. Looking at batanopride, the 6 mg/kg dose produced a fair amount of hypotension, while the 1.2 mg/kg dose really didn't have that much hypotension associated with it. Do you think that drug is worth continuing to look at in the lower dosage range?

Aapro: I'm not aware of all the data of the comparative studies between 1.2 and 6 mg/kg. What I've heard and what has been shown by the Danish study tends to indicate that there is a difference in efficacy between these two dosages. Right now, investigators were told and it has been told publicly at ASCO by Bristol Meyers, all investigations have been stopped because of this side-effect. The company is evaluating the side-effect profile of this compound and it is possible they will stop development of the compound. For these compounds we want to have a very good safety profile and it seems that with this compound we don't have it.

Gralla: Dr Martin, I have one question for you, since you have the newest antiemetic. It's interesting to see these new agents at different points of development. In the dog model you show that the LAS compound has 100 times the efficacy of metoclopramide, which certainly gave a lot of encouragement to its further development, yet the dosage you decided upon was about 10 times the dose. Is there a reason why there's this log difference, or should we have expected that?

Martin: Well, you know that these kinds of comparisons are artificial, because metoclopramide or LAS is 100 times more potent than another drug, but you must consider the therapeutic index more than the dose.

Gralla: Yes, but you presented us with the paradox that as you increase the dose in humans you saw a decrease in efficacy; yet in the dog there was safety, and the therapeutic index seemed to be in favour of the higher dose.

Martin: You're right, but these results are not very clear because it was not a randomised study, so it is very possible that the patients in the higher dose level are poor risk patients and patients in lower or intermediate dose levels are better risk patients. My personal impression is that we don't increase efficacy with more than 0.1 mg/m^2, but I don't think 0.4 is worse than 0.1.

Gralla: Dr Grunberg, in your very interesting talk you mentioned combining agents and you proposed the combination of metoclopramide with one of the 5-HT_3 receptors. Do we run into trouble if we consider that metoclopramide certainly has activity against 5-HT_3 receptors, that it may compete for the same receptor sites as the more specific agent? Might we paradoxically get poorer efficacy by combining granisetron or ondansetron with metoclopramide than would occur if we used only one of those, ondansetron or granisetron, alone?

Grunberg: Well, the point of that particular part of my talk was to suggest that there might be some mileage still to be gained by the combination of a 5-HT_3 antagonist and a D2 antagonist. If you choose to use low-dose metoclopramide as the D2 antagonist, that is one possibility. If that is a concern there are other pure D2 antagonists. The point I was trying to make was that I was not convinced that it was time to totally write off the D2 antagonists, particularly if some of them do show a certain amount of antiemetic activity that cannot be accredited to 5-HT_3 receptors blockage.

Gralla: But Dr Andrews, I thought you told us there really weren't any pure D2 antagonists.

Andrews: Some are purer than others. I think one of the things I would agree with is that we certainly should try that combination, but I would urge very much caution. Particularly with some of the 5-HT_3 antagonists because their CNS

behaviour effects are ascribed to modifications of dopamine which happens to have a D2 receptor there and if you get a D2 blocker in with a 5-HT_3 blocker that's trying to have an effect on dopamine levels in the same area of the brain, you may end up with some interesting effects, but until you try it there's no way of predicting.

Gralla: Can you tell us then how some of the D2 receptor antagonists might block emesis since they clearly have some efficacy.

Andrews: I would agree that they do. I think what it probably does is reduce some of the tone from the high levels of the CNS into the brain so the general effect is to reduce the level of arousal of the vomiting center. We know that emetic stimuli are additive if you give them a little bit of motion stimulus so they feel a little ill, then you hit them with a subemetic dose of apomorphine, they'll vomit, so there are obviously multiple inputs.

Gralla: So the role of D2 receptors would be to attenuate the emetic center. If that's true then. . .

Andrews: That would be my guess with haloperidol, but I think haloperidol's got other actions that may be relevant.

Gralla: So Dr Grunberg may have come on a good solution.

Grunberg: Again I would say, if Dr Roila tells us that within certain subgroups he can protect 90% of the patients with a combination of ondansetron and dexamethasone, perhaps the D2 blocker may not be the ultimate answer, but maybe the answer for another 9%.

Gralla: OK. We have a consensus on placebo. Do we have a consensus on the safety of the 5-HT_3 receptor antagonists, especially those that aren't benzamides. Do we feel that they are safer than metoclopramide?

Kris: I think you need to be a little more specific than that in terms of safety. If the safety you're talking about is extrapyramidal reactions, acute distonic reactions and akathisia, then it depends on what group of patients you're talking about.

Gralla: OK, for patients above age 30, are these agents safer?

Kris: I do not believe that there is good evidence that they are, using one of the best studied combination regimens of metoclopramide, dexamethasone and a benzodiazepine.

Gralla: Well then I'll define it a little bit more. It would appear that with metoclopramide, dexamethasone and lorezapam in several studies with high doses of cisplatin, defined as 100–120 mg/m^2, we can expect 60–70% of the patients not to have emesis. In a group that is over age 30 we can expect to see no more than 2% of patients have acute dystonic reactions, trismus or torticollus. We can expect about 3% of those patients to have akathisia. In fact, Roila has shown safety in his study using 4 mg/kg of metoclopramide. Metoclopramide in combination with other antiemetics can be given safely in a single high dose immediately before the cisplatin. It is relatively inexpensive. So for that group of patients over age 30, do we feel we have a lesser incidence of acute dystonic reactions and akathisia with ondansetron or granisetron? I would venture to say yes, there is a lower incidence. We have data on at least 3000 patients now and there appear to be no acute dystonic reactions.

Andrews: I'm just surprised that you expect there to be these sort of reactions, considering that most of the reasons they occur is the dopamine blocking effect. Clinically, the question has to be asked, but the answer is one you can predict before you even look at the patients, because of the involvement of the receptor.

Kris: I disagree that you could predict this result without treating a patient, I disagree with that.

Roila: I agree with Mark Kris because in 1985 with domperidone, when it was marketed, the company told us that no akathisia, no extrapyramidal reaction, no serious side-effects had been seen with domperidone, in experimental animals. But when we accurately studied the drug, we showed an impressive incidence of serious side-effects (mainly cardiac) and extrapyramidal reactions.

Gralla: So we have a consensus that there's a lesser incidence of acute dystonic or extrapyramidal reactions and akathisia with these patients treated with specific 5-HT_3 receptor antagonists. How about headache. Is that real? Is it a clinical problem? Dr Boyce.

Boyce: No, I think oncologists should give us a good description of that headache. Maybe we should call in some neurologists who are experienced in teasing out the patients. All we get back is headache–we can't describe it, it wasn't bad, that's not good enough. Headache occupies the time of lots of people in research, you've got to do a much better job of defining it. At the moment we know very little about it because it's not been described clinically.

Gralla: Well taken. Dr Grunberg?

Grunberg: In terms of our experience in observing the headache, except at the extraordinarily high doses of ondansetron, doses of 0.48, the headache was such that 325 mg of acetaminophen was enough to make it disappear. If we consider that the basic purpose of supportive care agents is to make the patients comfortable, our patients were comfortable, and headache was not a clinical problem. Stepping back to the previous question of dystonic reactions and akathisia, I include the anxiety reactions in this same area. I believe that most of the numbers that were quoted are for the first 24-h period and I would just like to remind everyone of an abstract that was presented at ASCO about 2 or 3 years ago. It was from a group from Long Island Jewish Hospital in New York, I believe, who actually did daily phone calls, in essence doing the same natural history for anxiety that Dr Kris did for delayed nausea and vomiting. If this problem was assessed over a 5-day period following the administration of high-dose metoclopramide, somewhere between 30 and 50% of the patients had some problem with anxiety. As we've questioned our patients in the later going, I certainly believe that these numbers are true. We have never seen a similar sort of problem with the 5-HT_3 antagonists that we've dealt with. If you're out looking for this problem, you must ask specifically because many patients will not spontaneously complain. They do not consider anxiety a side-effect and if they do, they assume that they are merely nervous because they just received chemotherapy. But I think this is a more significant problem and its lessening is an advantage for the new agents.

Kris: I couldn't agree with you more about the problem of anxiety in cancer patients, and actually it's something we've made some rudimentary steps in looking into. But the problem with that is, it's a very established and difficult methodology; to measure anxiety it must be done pretreatment with an approved scale and no out-patient, over-the-phone scale, to my knowledge, has been developed and validated against one of the many widely used and accepted anxiety scales.

Gralla: On headache, I think we have consensus that it's real, but that it's not as well defined as it ought to be. It's not much of a clinical problem so we might have trouble getting people to want to fund the studies to look into it more closely. Next

would be the question of hepatic toxicity, elevation of liver enzymes, that is seen with most of the 5-HT_3 antagonists. Do we think this is a problem and are we concerned about it?

Kris: The suggestion has been brought up that it's cisplatin that causes hepatotoxicity. I think we're in a unique position, with many people having done trials with high dose cisplatin and metoclopramide. It would be helpful to look at different studies to see if indeed cisplatin is the cause.

Gralla: Well, it's an excellent suggestion, but the randomised trial done in the United States did look at hepatotoxicity with the same doses of cisplatin. There was a significantly higher incidence of elevation of liver enzymes with ondansetron than there was with metoclopramide. It's probably a real phenomenon.

Joss: There is at least one clue from the comparative studies done with granisetron. There was no statistically significant elevation in the granisetron arms vs. the comparative arms.

Gralla: So, perhaps we're seeing some differences among these agents.

Grunberg: Paul Hesketh presented an analysis at the last ASCO meeting on the accumulated ondansetron data and suggested that the elevation of liver function tests showed a much better association with doses of cisplatin than with doses of ondansetron, which throws the whole problem back into question. We've drawn serial enzyme studies on some of our patients and have seen the elevations in patients receiving cisplatin without receiving 5-HT_3 antagonists.

Gralla: So, do we have much fear about the liver enzymes? So maybe I can get back to my original question. Is it fair to say that the 5-HT_3 receptors antagonists appear to be safer than metoclopramide?

Gandara: Maybe you should re-phrase it and ask if there's patient preference or preferred or some other term besides safer, maybe that's what people are balking at.

Gralla: Well, patient preference is an entirely different matter.

I'm looking for safety. From the profile I see, I believe the newer agents are somewhat safer to use in a variety of situations, especially in the younger patient. Does anybody want to strongly disagree?

Kris: Again, are you talking about numbers or about clinical significance?

Gralla: Clinical significance, not numbers.

Kris: I do not believe that for an older adult they're clinically significantly safer.

I again would add, for a 5-day treatment, and there is some data in our randomised trials, and for younger adults, the 5-HT_3 antagonists are clearly better drugs.

Aapro: I would certainly agree with Mark and not with you.

Gralla: For older patients, and for clinical significance, the newer agents have not clearly been shown to be clinically significantly different as far as safety's concerned. This is according to at least two of our panelists.

Grunberg: Now when you re-phrase the question, you have added an additional parameter, which was ease of administration. If safety and patient preference were put aside, I find when I'm giving high-dose metoclopramide to a middle-aged to younger population, I often use at least a four-drug combination, whereas with the 5-HT_3 antagonist where I do not need the diphenhydramine and where I may not even need the benzodiazapine to the same extent, I would say yes, the 5-HT_3 combination may very well be easier to administer. In that way there may be an advantage.

Joss: One additional parameter you haven't talked about is somnolence. I think it' clear that the 5-HT_3 antagonists have no somnolence as a side-effect.

Boyce: I'd like to give you an anecdotal comment regarding someone who's taken high-dose metoclopramide and felt very unwell for 24 h and then taken a 5-HT_3 antagonist and can't tell the difference with placebo. I certainly wouldn't queue up for high-dose metoclopramide.

Kris: Please don't blame metoclopramide for all these side-effects. It's very clear that if you give someone 20 mg of dexamethasone for another condition, they will also not sleep that evening and they also get gastrointestinal distress with that single dose, too.

Gralla: How about efficacy. If we look at the overwhelming majority of studies with metoclopramide as a single agent in patients receiving high-dose cisplatin, as Dr Grunberg, Dr Kris and many others have published, we find complete control to be in the 30–40% range. If we look at the studies that Fausto Roila was kind enough to summarise for us, generally with higher doses of cisplatin we find that usually for ondansetron as a single agent, upper 30s to mid 40s. We were asked about meta-analysis before; this is at least some attempt. Do we feel that there is a true difference between metoclopramide and ondansetron in efficacy? Comments, please.

Andrews: I think one thing you have to do is to not lump the 5-HT_3 antagonists together.

Gralla: Well, I was just talking about ondansetron.

Andrews: It may not necessarily be the best. I think the difference is not that great, particularly against metoclopramide. It's worth having if you're in that 10% of patients that's going to benefit.

Roila: In the three trials published, ondansetron showed superior responses with respect to metoclopramide, less toxicity and was preferred by the patients. I think that according to these results, ondansetron is probably superior to metoclopramide alone, but the problem for me is that metoclopramide alone is not the standard treatment. Before giving guidelines for the best antiemetic treatment for prevention of emesis induced by cisplatin, we must consider that the antiemetic treatment of choice is still a combination of 3 mg/kg × two times a day of metoclopramide or only one administration of 4 mg/kg of metoclopramide plus dexamethasone plus diphenhydramine or lorezapam. This is the standard and this is the treatment vs. which ondansetron plus dexamethasone has to be evaluated. Only this can resolve the problem of best treatment.

Gralla: I think those points are very well taken. I'd like now to conclude. I know there are many topics that only a dedicated audience could listen to any longer, and I really appreciate your attention. In closing, I think it's very appropriate that we have had this conference, perhaps the most thorough on antiemetics and new antiemetics ever conducted. It's most appropriate that this conference occurred in Perugia. This institution has had a major role in the definition of combination regimens and the dose–effect relationship of different regimens, as well as the development of new agents such as ondansetron and ondansetron and combinations. Not only have we come to a lovely place to have a conference but also a center that has contributed by strength of their work and by their leadership. Certainly what we've heard is a multinational approach. Investigators have approached this same problem in different ways. This conference may be ahead of its time. What we've heard today will certainly contribute to

the publications through 1992. I'd like to thank the very hard work of Maurizio Tonato and his group for putting together such an excellent program.

Tonato: I need an extra consensus from the panel, Richard. We have a prize from an Italian newspaper that should be given to an Italian researcher in this field and so I propose Fausto Roila as the recipient and I'd like for the panel to support this choice.

Gralla: I'd like to second that.

Eur J Cancer, Vol. 29A, Suppl. 1, pp. S51–S58, 1993
Printed in Great Britain

0964–1947/93 $6.00 + 0.00
Pergamon Press Ltd

Quality of Life Assessment in Individuals with Lung Cancer: Testing the Lung Cancer Symptom Scale (LCSS)

Patricia J. Hollen, Richard J. Gralla, Mark G. Kris and Lisa M. Potanovich

This paper presents the continued development and multi-institutional testing of an instrument focusing on measuring the physical and functional dimensions of quality of life. It emphasises evaluation of symptoms associated with lung cancer and their effect on activity status. The Lung Cancer Symptom Scale (LCSS) is a disease- and site-specific instrument which has both a patient and an observer (health care professional) form. The patient scale required 8 min to administer and the observer scale 2 min. The readability index was second-grade level for the patient scale and ninth-grade level for the observer scale. Content validity revealed a mean of 96% agreement for all major symptoms among 52 experts surveyed (confidence interval = 86–99%, $P = 0.05$). 69 patients with non-small cell and 52 patients with small cell lung cancer confirmed that the symptoms matched their experiences. Interrater reliability showed consistency for all items but one among 21 raters at eight institutions; that one item was consistent for 20 of the 21 raters. Similar results were found on a 9-month interval replication. Using the Kappa statistic to estimate extent of agreement for repeated interrater reliability, almost perfect agreement was obtained (mean coefficients, 0.95–0.98). Using the same rule of agreement as for Kappa (± one category) intrarater agreement was 95–100% for all 21 raters. Past test re–test reliability indicated high patient reproducibility for 52 patients ($r > 0.75$, $P < 0.01$ for all items). We conclude that (1) the LCSS demonstrates good feasibility, reliability, and content validity, (2) high interrater reliability indicates utility in multicentre trials, and (3) continued testing for internal consistency, construct validity and criterion-related validity is warranted.

Eur J Cancer, Vol. 29A, Suppl. 1, pp. S51–S58, 1993.

INTRODUCTION

IN ADDITION TO reporting response and survival rates, the need to determine the effect of cancer and its treatment on quality of life is clear. Disease-specific instruments, detecting differences in patients with malignant disease, are one method of improving the assessment of subjective parameters or "quality of life" in clinical trial research in oncology [1, 2]. Although generic quality of life instruments applicable to any chronic disease population have been developed, the trend is to develop measures specific to the cancer population [3]. Moreover, development of specific instruments focusing on a particular malignancy is becoming more common. Several problems exist with many of the currently available instruments, including a lack of focus on the clinically important area of symptom management, long and cumbersome questionnaires and an absence of adequate psychometric testing to determine the reliability, validity and utility of the instruments.

Initial development and testing of the Lung Cancer Symptom Scale (by R.J. Gralla and M.T. Burke) began in the mid 1980s [4, 5]. It was specifically designed to address the issues of palliation and symptom control in evaluating patients receiving new chemotherapy regimens. The favourable initial psychometric properties of the Lung Cancer Symptom Scale (LCSS) encouraged continued systematic development to

Correspondence to P.J. Hollen.
P.J. Hollen is at the University of Rochester, 601 Elmwood Avenue, Rochester, NY 14642; R.J. Gralla is at the Ochsner Cancer Institute, Ochsner Medical Institutions, 1516 Jefferson Highway, New Orleans, LA 70121; and M.G. Kris and L.M. Potanovich are at the Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, U.S.A.
Received 30 Jan. 1992; accepted 8 May 1992.