Panel Discussion 2

M.		Tonato
----	--	--------

Jackson: Jackson, Royal Perth Hospital, Australia. I have a question for Dr. Kaasa. In the presentation of information to the patient, there is a considerable investment of time. I understood you to say that you felt that as far as quality of life questionnaires are concerned, that there should be a separate coordinator in this area to do that job. I wonder who you think that should be, a nurse, social worker, a physician? And also I wonder if you would say just a little about the difficulties in establishing the reliability and validity of these questionnaires?

Kaasa: I'll try to pick up the last question first, to establish the validity of these questionnaires. I totally agree it's problematic, because we do not have any gold standard to assess them against, so the validation procedures have to be indirect. This means we have to use several methods indirectly to measure the validity of the instruments. With regard to the reliability of the instruments, it is possible to compare different raters, and also to look at the internal consistency, this can be done by looking at different questions measuring the same concept. With regard to your first question, about organising the study. I do not think it's important who is responsible for the quality of life part of the study. What is important is that the person is dedicated to it, and that patients receive their questionnaires. But I think if I understand your point correctly, you also raise the question about biasing patients filling in the questionnaires. For example, in one centre, a physician may give the questionnaires to the patients, in another centre it may be the nurses. This may bias the results, so we have to be aware of such problems too.

Tonato: Dr. Kaasa, I agree with your suggestion, not to make your own questionnaire, but I think there are differences in the knowledge of the disease by different patients that don't allow us to apply the same questionnaire in every situation. I would like your comment on that.

Kaasa: Yes, with regard to the culture differences, I think we may have problems in interpreting the results from, for example, the southern part of Europe to the northern part of Europe, because as you say the information patients have about the disease is different. Within the EORTC, we found some cross-cultural differences. The major part of the cross-cultural difference is between the northern and southern part of Europe. Between the United States, Canada and the northern part of Europe there was hardly any difference at all.

Anonymous: I have a question for Dr. Kaasa about the questionnaire. I think it's very important to do research with interview and observations. The Rotterdam questionnaire has 22 physical measures, 8 functional and 8 psychological. So I wonder what kind of quality of life we are measuring with such questionnaires.

Kaasa: If I stated that the only way of assessing quality of life is to use questionnaires, I think you misunderstood me. What I meant to say was that in multicentre clinical trials it is optimal to use questionnaires. I totally agree with you, if you want to get more details of the patient's perceptions of quality of life, you should use interviews or observations. With regard to the content of the different questionnaires, I think, for example, the Rotterdam Symptom Checklist is somewhat skewed against the physical symptoms.

Tattersall: Dr. Tattersall from Sydney, Australia. Dr. Soukop, I understood that your study referred to patients with advanced breast cancer and you appeared to show quite convincingly that the ondansetron regimen was superior. Do you have any similar data or are there any data about the use of these drugs in adjuvant therapies?

Soukop: This, as far as I know, is the only trial that has looked at the data in this sequential way, and I think that's why it is particularly interesting; but I would imagine that we might well find there are very similar trends looking at different groups of breast cancer patients.

Smyth: I think Martin Tattersall raised a very interesting point because the psychological setting of women having adjuvant therapy is very different from those having advanced therapy. The situations might be similar, but I think it's an assumption that one can't afford to take. I don't think anyone has done a substantial adjuvant study [Editor's note: Post meeting this was analysed, see p. 297].

Anonymous: Just for a little clarification, a lot of us don't use alizapride and perhaps you'd like to comment on the fact, as I understand it, that it's quite widely used in France, and that was the reason for using it as a control for the study.

Depierre: Yes, it's the main reason for these trials, these drugs and methylprednisolone are widely used in France in particular, and we thought it was very interesting to test ondansetron not only against metoclopramide but also against alizapride, which is similar.

Tonato: Yes, I think this raises the ethical issue though of a suboptimal comparative treatment when studying a new product. Alizapride has been shown in 3 controlled trials to be clearly inferior to metoclopramide. I would like a comment from Dr. Olver on the ethical situation of studies comparing placebo versus a new drug in highly emetogenic chemotherapies.

Olver: I don't think it is ethical to use a no treatment control arm in studies of highly emetogenic chemotherapy. We have an arm such as metoclopramide/dexamethasone that's effective; it's not as effective as we'd like and that's why we can do studies at all, but I think the most effective arm you have has to be your control arm. You can't leave patients who are almost 100% sure of vomiting, which is the situation with cisplatin given at 100 mg/m² without any anti-emetic drugs to cover their chemotherapy.

Smyth: Can I just comment on that. I understand the point of the ethics that you make, indeed I myself have been quite critical of some of the published literature using placebo, and I think that it's unacceptable if you have moderately effective anti-emetics to do placebo-controlled trials. But my understanding of the trial against alizapride was that people were interested in comparing a new regime with something which they were comfortable with and used as their conventional standard therapies. And it's my experience, certainly in Britain, that it's actually quite hard to get people to change their attitudes and change their routine practices, and therefore I think there probably is an ethical point that the way to change clinical practice is to set the new treatment against what people are currently using.

Olver: I would agree with that. If that is the standard practice, then that should be the control arm. However, I think the benefit of keeping up with the literature is to make sure that your standard practice is current, and I think that's an ethical responsibility of doctors who treat cancer as well.

Heslop: My name is Hilary Heslop and I am a nurse on the postoperative ward at the Norwegian Radium Hospital. As chemotherapy is administered to patients after radical mastectomy postoperatively, how do you do trials taking into account postoperative nausea?

Smyth: I think that is very difficult, because the actual degree of emesis will depend a lot on certain patient factors, but also on the particular operation and the particular sequelae of the

surgical procedure. It will also vary quite a lot with the different types of anaesthetic regimes that are used. So I think that there are a lot of methodological problems in standardising trials for postoperative vomiting, but I know that there is a great deal of interest in that area particularly amongst anaesthetists. And I think that it is possible to design studies, particularly in a single centre, where at least you can standardise anaesthetic practice and take cohorts of patients who are having routine procedures, cholecystectomy, for example. I think it's very much more difficult to do that type of research on a multicentre basis because of all the other variables of the operative approach, the anaesthetic practice and so on.

Brown: Yes, if I could add to that. We have been carrying out a very extensive clinical trials programme to look at the efficacy of ondansetron in postoperative nausea and vomiting, and indeed placebo-controlled studies do show evidence of activity. But I wasn't quite sure whether your question was related to postoperative nausea and vomiting or the combination of that with chemotherapy. What was the problem?

Heslop: It is the combination with chemotherapy in patients undergoing radical mastectomy. They are administered chemotherapy postoperatively, immediately after the operation, and we have great problems controlling the nausea, and often we don't know whether it is the chemotherapy or the anaesthetic which is causing the nausea.

Brown: Well, I certainly agree with John then that there are major problems in designing a study that will answer those 2 questions at once, but what I can tell you is that this drug is effective in postoperative nausea and vomiting.