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Discussion at the Satellite symposium: Ifosfamide in gynecological tumors*

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Discussion, part I: cervical and ovarian cancer

Wiltshaw (UK): Are there any questions about the papers on cervical and ovarian cancer?

Hanády (Hungary): I would like to start with the presentation of Lund, because I am so excited with these excellent response data. I have to raise the question of survival. I know it is too early for an estimation of survival; nevertheless, you may have some idea as to which survival times can be expected in patients who show such good response rates.

Lund (Denmark): Well, it is quite correct that our median observation time is just 14+ months at the moment; the longest observation time is 21 months. As we have not really looked at these data yet, we think that it is too early.

Wiltshaw (UK): In that connection, may I ask you if you think that the response rate with the two platinum compounds alone, which you gave first, is significantly different from the new response rate with the addition of ifosfamide?

Lund (Denmark): It is not significant, not at the 5% level, but it is markedly increased with ifosfamide.

Willemse (The Netherlands): Dr. Lund, may I pursue the question of the first schedule you used, i.e. carbo- and cisplatin together. Did you have to reduce the dose as often as in the second study?

Lund (Denmark): When we decided to combine it with ifosfamide, we had to reduce the carboplatin dose. In the first trial, we gave 300 mg/m^2 on day 1, and in the second study, 200 mg/m^2. It was not until the sixth cycle that the median dose had been reduced to two-thirds of the planned level; in the third cycle of the first trial, the median dose was about 90%. That means that dose reduction was more marked in the second trial.

Wiltshaw (UK): Dr. Willemse, bearing in mind our response rate in patients on ifosfamide alone, given in a manner similar to the one you used, do you think that our response rate after three courses was due to the fact that we did not give more than three courses? Do you have any idea as to how long it took you to achieve a complete response on ifosfamide alone in relapsed patients?

Willemse (The Netherlands): We did the evaluations after every second cycle. Therefore, at least the progressive patients were progressing after two cycles.

Wiltshaw (UK): Yes, but how long did it take to get the response?

Willemse (The Netherlands): I think that the partial responders were already responding after the second cycle, and two went on to a complete response. The response was seen as soon as after the second cycle.

Audience (Italy): My compliments to Dr. Lund. Is it likely that similar results with less toxicity might be obtained with a combination of cyclophosphamide and cisplatin or carboplatin? What is your opinion?

Lund (Denmark): We chose ifosfamide because this drug is renowned for its modest hematologic toxicity as compared to cyclophosphamide. I do not know whether toxicity might be lower. If one combines carboplatin and cisplatin, thrombocytopenia is expected. Therefore, I do not think that it would make that much difference.

Willemse (The Netherlands): I think Dr. Lund is right. We are giving our patients carboplatin and cyclophosphamide

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at the moment, and thrombocytopenia is a real problem. In my opinion, the use of ifosfamide may prevent this problem.

Audience: Dr. Tobias, what were the causes of the two deaths each in the radio- and chemotherapy groups?

Tobias (UK): In the radiotherapy group, one patient died approximately 10 days after completion of radiotherapy, for no obvious reason. We were not sure why, but we felt that we had to include this case as a radiotherapy-related death. The other was a septic death caused by a bowel perforation. In the chemotherapy group, the same number of deaths occurred. These were septic deaths; one was a clear-cut case of septicemia, and the other one involved a patient who developed acute pyelonephritis and was not prepared to come into hospital and be treated for that. This patient died at home. We had the same number of deaths in each arm, but we think they probably occurred for slightly different reasons. The number of other prominent bowel problems was also similar, and they involved, of course, essentially radiation proctitis.

Audience: Dr. Tobias, sequential chemo- and radiotherapy in head and neck carcinoma did yield more satisfactory results. What do you think about cervical carcinoma? If chemotherapy is given sequentially with radiation, results might be better, but what are the complications to be reckoned with?

Tobias (UK): This is indeed a very difficult question because not everybody would agree even with your first statement about the appropriateness of sequencing with chemo- and radiotherapy in head and neck cancer – it is very debatable. In general, if one is going to use combinations of intensive chemotherapy and intensive radiotherapy, I myself prefer to give the chemotherapy first – particularly in carcinoma of the cervix, where one is essentially delivering a very large volume and high dose of pelvic irradiation. This is clearly likely – at the very least – to render the patient more susceptible to chemotherapy-related problems. I think that is rather a good reason to give the treatment the way we chose to do. Therefore, I would really argue the point from a purely pragmatic basis – at present, at any rate. Of course, theoretically the question remains a very interesting one.

Willemse (The Netherlands): I would like to comment on the study of Dr. Harper concerning the efficacy of ifosfamide. My point is that Dr. Harper's study is the third one to show a difference in the efficacy of ifosfamide if the mesna scheduling is changed. In the earlier studies of ifosfamide in ovarian cancer remission, percentages of about 60%–80% were found. When mesna was added at the beginning of the 1980s, efficacy seemed to drop somewhat. Wist did a study with continuous 24-h infusions of ifosfamide in soft-tissue sarcoma in a second-line setting, comparing mesna given as a bolus in a total of 2.8 g vs the three-fold amount of mesna given continously over 24 h. This was not a randomized study. All of his four responders were in the group that received mesna as a bolus.

Dr. Antmann recently published results in soft-tissue sarcoma. She first gave ifosfamide over 4 h on 4 consecutive days, combined with mesna given as a bolus. She then went on with ifosfamide given continously with mesna; response dropped from 24% to 9%. I think that we should be very careful with the administration of mesna on a continuous basis; it might have an adverse effect on ifosfamide efficacy. I do not know if Dr. Harper would like to comment on that, yet this might be an explanation for the differences seen in the two phase II studies.

Harper (UK): Thank you very much for the point that is being made, I think, by a number of us and in other tumors as well. Our initial sarcoma report, of which Dr. Wiltshaw was the author, was on ifosfamide given in exactly the same way as was done in our initial cervix study. The subsequent EORTC study to which you referred used ifosfamide over a shorter period of time. In the BIP study, ifosfamide was also given over a shorter period of time. In the BIP study, we were also giving a lot of mesna, but we were clearly seeing a lot of responses as well, because the response rate in relapsed disease, as in Dr. Tobias' second study (BIP), was very high indeed. I think that the answer to this question is still open and we should watch this carefully.

Brade (FRG): I think that I have to comment on this dose relationship between ifosfamide and mesna. Ever since the introduction of mesna, there has been the question of a possible interaction of mesna and ifosfamide. The differences found in the studies presented today do not exclusively concern the mesna dose, but involve the ifosfamide dose and schedule as well. I got the impression – particularly from Dr. Harper's presentation – that the fractionated ifosfamide dose might be more effective than continuous ifosfamide infusion. As far as we know from animal experiments, the mesna dose can be increased to up to 20 times the ifosfamide dose without interfering with ifosfamide's efficacy. We looked at the equilibrium constants of the possible complex of activated ifosfamide, 4-hydroxy ifosfamide plus mesna. By this means one may conclude, as did the FDA in December 1988, that no interaction of mesna and ifosfamide takes place in the serum that might affect the efficacy of ifosfamide.

I completely agree that we have to find the optimally or minimally effective mesna dose for the large variety of ifosfamide schedules we have today. In the past – this might represent a difference as well – the most common schedule was a fractionated dose of ifosfamide, in most cases in the range of 1.5 g/m^2 up to 2.4 g/m^2 given on 5 consecutive days, combined with the classic mesna dose of 20% of the ifosfamide dose, given at 0, 4, and 8 h. With this schedule we had the data discussed in ovarian cancer and quoted as historic data. In my opinion, comparison is difficult due to the variety of ifosfamide schedules. Furthermore, response and selection criteria as well as the criteria for prognostic factors are now completely different from what they were in the past.

Audience: After the BIP neoadjuvant treatment you obtained complete responses. Do you think that surgical pro-

cedures would be feasible then? Most of these patients are young.

Tobias (UK): The question was whether these patients would then become suitable for surgery. I feel rather strongly that the answer is no. It seems to be far too premature to take the view that this chemotherapy is so effective in down-staging that a patient that one would normally regard as being inoperable should now be regarded as oprable. You know, that may turn out to be the case if this study really does hold up well and we can demonstrate a real alteration in response duration and survival.

I make no such claim at the moment, absolutely none. However, if we can substantiate that it is the kind of question I guess one can ask. However, at the present time I would say very strongly, in my own view, that patients who have been felt to be inoperable in the first instance, and that usually means – in the UK, at any rate – patients with bulky stage disease of II A or II B and beyond, I would regard those patients as still being inoperable, even when they respond well to BIP. I do not know how one would answer that question in 5 years' time, but that is how I would answer it today.

Audience: However, your CRs are not surgical but rather clinical CRs. Are your complete remissions histologically proven?

Tobias (UK): No, they are not. That is correct.

Discussion, part II: breast cancer

Tischler (Israel): Dr. Gad-El-Mawla how long did you continue the chemotherapy in patients who went into complete remission?

Gad-El-Mawla (Egypt): The average was five courses, but some of these patients received seven or eight courses; I do remember that.

Mouridsen (Denmark): Of your 25 patients, 14 were premenopausal. How was that defined? Were they still menstruating?

Gad-El-Mawla (Egypt): Yes, they were.

Mouridsen (Denmark): Did they stop menstruating during treatment?

Gad-El-Mawla (Egypt): No, they did not have any amenorrheas during treatment.

Mouridsen (Denmark): That means that they had prior CMF, and then ifosfamide, methotrexate, and 5-FU, and were still menstruating. All of them?

Gad-El-Mawla (Egypt): Yes, all of them.

Bauer (Austria): Dr. Sanchiz, you told us that 22 of your 27 patients had been pretreated with more than two chemotherapies. Does this include the adjuvant treatment as well?

Sanchiz (Spain): Of 28 patients, 24 had had previous adjuvant therapies.

Bauer (Austria): It did not get whether your therapy was third- or second-line treatment.

Sanchiz (Spain): In approximately 25 patients it was second-line treatment, in the other cases, it was third-line treatment.

Audience (Turkey): Dr. Sanchiz, you mentioned that ifosfamide and mesna were given in the same solution. Is there a possibility for inactivation of fluorouracil?

Sanchiz (Spain): I do not know. All our patients were treated with ifosfamide plus mesna. Maybe the addition of 5-FU into the same infusion might give rise to inactivation of 5-FU.

Brade (FRG): Dr. Sanchiz, the schedule you used seems to be very new. As I understood, you used 6 g/m^2 + 6 g/m^2 mesna as a continous infusion over a period of just 4 h, and you did not have marked toxicity, with the exception of leukopenia. Did you see other toxicities as well?

Sanchiz (Spain): With 4-h infusions toxicity might be increased, but we presented another study with 24-h infusion of ifosfamide, which gave rise to similar toxicity.

Wiltshaw (UK): I am a novice in the treatment of breast cancer. Can you tell me what place ifosfamide has in second- or third-line treatment? The response rates you are all getting are roughly similar. Does this mean that all of the responses are due to the ifosfamide and not to the other drugs you have been giving, or that ifosfamide is not adding to the results you have been giving? It seems that with single agents you are still getting a response rate of about 20% of 25%. What is the position for ifosfamide?

Sanchiz (Spain): I think that the position of ifosfamide is in combination with other drugs as first-line therapy.

Langenbuch (FRG): I have only two patients to talk of; both of them were in the same situation before we started ifosfamide. Therefore, in my opinion, the most effective drug in these two cases was epirubicin. The CA-153 levels decreased after the first three chemotherapy cycles.

Höfeler (FRG): There are some data that enable us to answer this question Dr. Gad-El-Mawla used ifosfamide; her patients were pretreated with CMF and then got IMF. Therefore, the only difference was the ifosfamide; in the end, she had a remission rate of 25%, and the ifosfamide

was responsible. Most of our own patients had been pretreated with cyclophosphamide and epirubicin. When we started our study, to avoid losing the possible effects of methotrexate and 5-FU, we added ifosfamide. We were not that much interested in what ifosfamide does as a single agent; rather, we wanted to give effective therapy to our patients.

Manegold (FRG): In my opinion, ifosfamide should be used after cyclophosphamide pretreatment as a palliative therapy in otherwise heavily pretreated patients. Ifosfamide may perhaps replace cyclophosphamide because of its more favorable toxicity profile in first-line chemotherapy for breast cancer.

Gad-El-Mawla (Egypt): I think the answer to your question is to start with ifosfamide either alone or in combination as first-line treatment.

Mouridsen (Denmark): Based on the data presented thus far, your question is quite difficult to answer. The data presented today, and that in the literature as well, indicate that there is no doubt that ifosfamide is active in heavily pretreated patients, with the pretreatment also including alkylating agents such as cyclophosphamide. In my opinion, this is the most fascinating feature of this drug. Most important are the studies on the possible cross-resistance of ifosfamide and cyclophosphamide. In the future, as many patients will receive adjuvant CMF, it is crucial to develop new drugs that are non-cross-resistant with cyclophosphamide. The question is whether ifosfamide's proven activity in patients with prior CMF treatment might simply be due to a dose-response relationship. What would we expect in patients who had received normal CMF doses if we gave them a second course with high-dose cyclophosphamide in an infusion? I do not think that we have data on that. Does remission reduction simply involve a dose-response relationship for an alkylating agent, or are cyclophosphamide and ifosfamide non-cross-resistant? Without more data concerning this problem, your question cannot be answered. There is another problem in this regard. What role does mesna play in the activity of ifosfamide? Does mesna inhibit its anti-tumor activity to some extent? Are we convinced by the available data that mesna does not interfere with the anti-tumor activity?

Höfeler (FRG): I do not have hard data on this topic. However, if you give mesna as a single shot, excretion via the kidneys is so fast that there is not much time for interaction of mesna and ifosfamide at the serum or cancer level.

Klein (FRG): The diversity of ifosfamide and mesna schedules used is rather striking. From a biological point of view, proliferation of the tumor being treated is important. Dr. Sanchiz, you found in your patients median disease-free survival of 23 months. These tumors obviously had very low proliferation rates. In another paper, mean survival of 6 or 8 months was reported which may be due to rapidly proliferating tumors. What is the rationale for the ifosfamide-mesna schedules presented today?

Gad-El-Mawla (Egypt): The answer is to go back to the pathology of these tùmors and correlate the response to the pathology.

Langenbuch (FRG): We have been using the 5-day ifosfamide schedule in other tumors as well. When we started this study 2 or 3 years ago, we chose this schedule because of the toxicity we have to reckon with in pretreated patients.

Höfeler (FRG): We chose our schedule for practical reasons: we treated our patients on an outpatient basis. This is recommended for breast cancer patients, as treatment is palliative and the patients should be able to live with their families as much as possible. Treatment was thus given for just 1 day and the patients went home after that.

Pfleiderer (FRG): I would not agree with the statement that a remission rate of 20% achieved by ifosfamide after cyclophosphamide pretreatment is indicative of better activity for this drug. In relapse cases you get similar results by repeating the same drug. In my opinion, none of the studies presented demonstrated conclusively that ifosfamide is superior to cyclophosphamide. Based on the data available, would you switch from CMF to IMF, say, for adjuvant therapy? We know that repeating CMF treatment in patients relapsing after adjuvant CMF therapy gives rise to relatively high remission rates.

Höfeler (FRG): In my patient population there were no relapses; these patients progressed while on chemotherapy. In 43 cases there was progression during chemotherapy that included cyclophosphamide; in those patients we got this response rate. There is no denying the fact that in patients treated successfully with a given drug, the same drug is helpful in treating a relapse; however, our patients showed progression during cyclophosphamide therapy.

Langenbuch (FRG): We tried to define the role of ifosfamide in a truly palliative setting after heavy pretreatment with cyclophosphamide. Of course our data, do not represent evidence for the superiority of ifosfamide in first-line therapy or even adjuvant treatment of breast cancer.

Bauer (Austria): Is high-dose ifosfamide as third-line therapy not a rather drastic approach for breast cancer patients who in around 30% of cases suffer from severe nausea and vomiting and show a high level of encephalopathy? Furthermore, ifosfamide is nephrotoxic. Do you think this can be justified for a survival period of 4 months?

Langenbuch (FRG): No, that is what I tried to show. There is tremendous myelotoxicity, and one has to be very careful. Such treatment is recommended in certain cases; the decision has to be made individually. On the other hand, GI toxicity is not the real problem. Some patients insist on being treated, and after this kind of pretreatment you have to look for something different; that might be ifosfamide. There is no doubt that this is a toxic treatment, particularly when used in a combination. It should be used as a single agent after such heavy pretreatment.

Mouridsen (Denmark): The question you raised is very general. We might choose not to discuss it at all, or we might discuss it for 2 h. Actually, I think that we should not discuss it at all, because we are running out of time. To keep on schedule, I will close this part of the session.

What can very briefly be concluded about ifosfamide in advanced breast cancer is that the drug is definitely active in breast cancer. There are still open questions, particularly regarding the degree of cross-resistance with cyclophosphamide. There are even more questions as to dose and schedule as well as dose-response relationship and schedule. The drug merits further investigations, but there is still a lot of work to be done.