Discussion

Dr. Trump (Madison, Wis.): Did you notice any difference in the dose of AG[1] administered and response rates, since you mentioned that several patients got lower doses, Dr. Murray?

Dr. Murray: No, we monitored DHEA sulfate, as I said. In fact, there was one patient who received 375 mg AG only (1.5 tablets) who had a 9-month response.

Dr. Ingle: I am interested in your first conclusion, which is that AG is the treatment of choice as second-line treatment after TAM in TAM responders. If you look at past experience, treatment with some of the more conventional agents, such as DES, has produced a response rate at least of the same order. That is, in our study we had a 45% response rate. And I think I have raised the question whether or not, in the absence of a comparative trial, one could lay a firm basis for your conclusion.

Dr. Murray: That is a legitimate thought. Obviously, these results need to be confirmed by others, but so far the other studies show similar results.

Dr. Santen: If one accepts the hypothesis that AG is working predominantly through inhibition of aromatase, is it appropriate to adjust the dosage based on the DHEA sulfate levels, rather than perhaps on the levels of estrogen?

Dr. Harris: We chose to measure DHEA sulfate because it is very easy to measure, whereas estrogen is not. As I understand it, the aromatase inhibition occurs at a lower level than that of desmolase; so if one has inhibited desmolase and DHEA sulfate has dropped, we would assume that estrogen levels had also fallen.

Dr. Troner: I would just like to echo the opinion about AG being used after TAM. I also agree that trials between AG and DES are clearly indicated. Have you looked at how quickly responses are seen in any of these groups? Were there any differences in rapidity of response in the patients who had not responded to TAM?

Dr. Murray: We really did not look at rapidity of response. The first full assessment with repeated skeletal surveys and liver scans was at 3 months. We did not actually ever make a decision before 3 months.

Dr. Segaloff: We are facing an entirely different population of patients than many of the studies being referred to with other drugs, where everyone was treated across the board. We are selecting a group of patients who are more likely to respond and to survive longer. Before we get excited about percentages, we must count every patient in the denominator. I would also like to point out that very little changes the growth rate of tumors as much as it appears. If you look at bone lesions, more than 3 months are required to show progression. Half of them are going to appear to be stable even if you do nothing. And if you are looking at them the same way to produce progression, I suspect you would have many people in 3 months who appear to be stable. So I would plead for comparative studies with other drugs.

Dr. Harris: In our randomized study, there are no patient exclusions, and all the percentages of patients include all the patients entered. Secondly, we found the difference in objective response in bone secondaries was nearly double with AG compared to TAM. This is what Dr. Lipton also found, disregarding any argument about stabilization of disease. The third point on disease stabilization is that patients with no change at 3 months and pain relief do survive as well as those with partial response.

Dr. Smith: These patients who have bone pain are all already on these drugs you are talking about—dimorphine or whatever. We then treat them all with a form of therapy, and some of them have pain relief such that they can come off the other drugs. These people, who can come off the other drugs, survive more than twice as long as those who must continue. It is not that we are not using dimorphine; the progressive disease group is on these drugs. I fail to understand what the problem is here. You have got a treatment which in one group of patients means you can take them off these drugs and they live twice as long. Surely that is effective treatment.

Dr. McGuire: I think what Dr. Segaloff is pointing out is that maybe the patients with what you call stable disease have a less agressive tumor and would do better anyhow; that the effect of your drug is similar to the old L-dopa test. When you get bone pain relief, that is a hormonally responsive tumor; you are using a central nervous system-active agent. I am not sure we will resolve this issue today, but I think Dr. Segaloff just wants to point it out so that those of you analyzing these trials will keep it in perspective when evaluating stable disease without having objective evidence that the disease was actually progressive prior to starting the therapy.

Dr. Smith: What is evident from our discussions is that it is not just a 30% objective response rate but that another 20 to 30% of patients achieve stable disease. Now whatever that means, whether they would have done well anyway, it is significant in terms of survival. When you put all that together, you've got 50% who achieve benefit. We do not want to get into the argument of endocrine therapy *versus* chemotherapy because that is silly; we know both forms of treatment have a role to play. But until now we seem to be apologetic about endocrine therapy, as if it is not so good because the response rate is lower.

Dr. McGuire: I am sure no one on the panel is embarrassed about the benefits of endocrine therapy. I suspect most of those gentlemen would not like to destroy the credibility of the data by using nonobjective criteria to show it is just as good as chemotherapy, because that will do their studies as much harm as good. But let the panel speak on that question.

Dr. Murray: We still must report objective remissions and really take the data on that, although we know 50% of the patients appear to benefit. But if we are going to make comparisons, at the moment I think we still have to stick to objective remission. However, I would emphasize that these treatments are very well tolerated and most patients feel well. The treatments are not toxic most of the time as is chemotherapy.

Dr. Ragaz: I have a specific question for Dr. Harris, but in formulating the question I would like to mention 2 observations. One is an observation made in the Noble rat system that oophorectomy or adrenalectomy was effective in causing remission; however, if the tumor subsequently progressed in the absence of estrogens, the tumor became autonomous to hormonal manipulation. But if the same experiment was performed with estrogen pellets remaining *in situ*, upon subsequent relapse and oophorectomy or adrenalectomy in the presence of estrogens, the tumor still remained hormone sensitive. Dr. Noble and his group suggested that complete abolition of estrogens therefore, although initially beneficial, may subsequently precipitate an autonomy. The second point is the suggestion of mutations from the state of sensitivity into state of resistance which comes into the denominator resulting in resistance. In view of these observations, I am trying to find an explanation for your data in which you showed a fairly good response to AG after TAM failure but very minimal or low response to TAM after AG failure, suggesting that if experimental data on AG show more effect in abolishing estrogen source, hormonal autonomy would not subsequently be precipitated.

Dr. Harris: That is a very interesting estimation. It is difficult to know in quantitative terms because we have measured these TAM suppressions in all our patients and it suppressed about 50 to 60%, so there are still very significant amounts around. I do not know whether the degree of estrogen depletion in the Noble experiments is comparable to that in these patients. It is an interesting possibility.

Dr. Paridaens: You have observed a higher response rate to AG when given after TAM as compared to the reverse sequence of treatment. Do you not feel that several responses in patients treated with AG could be ascribed to a withdrawal response to TAM since this compound is likely to provoke a flare; it has estrogenic effect?

Dr. Harris: We tried to leave a gap between crossing over. In cases of bone pain that was not possible. The objective response on TAM withdrawal in people with progressive disease is very low indeed.

[1] The abbreviations used are: AG, aminoglutethimide; DHEA sulfate, dehydroepiandrosterone sulfate; TAM, tamoxifen; DES, diethylstilbestrol.

Dr. Paridaens: TAM has a very long half-life, 15 days, and the metabolites also. Thus, one would have to wait a long time before observing such a response. Does anyone have experience of withdrawal response to TAM? I have seen one documented response in the literature.

Dr. Gale: In our program, head-to-head, TAM *versus* AG, there were 2 patients in the trial who had no response to treatment and had a withdrawal response.

Dr. Santen: The studies presented this morning seem to show 2 differences between AG and TAM. The cross-over comparisons seem to be different. Patients on TAM first respond to AG secondarily, but not vice versa; and patients on AG seem to have higher bone responses. This would tend to suggest a different mechanism of action of the 2 agents, and yet, simplistically, we would think that AG suppresses estrogen production and TAM estrogen action. I would like to raise the hypothesis that in one sense AG seems to be working as hormone-ablative therapy—no tumor flares, no hypercalcemia, and no withdrawal responses—whereas TAM seems to be acting somewhat similarly to hormone-additive therapy, with tumor flares, hypercalcemia, lesser response in bone healing.

Dr. Lipton: Later, Dr. Wells will present our combined experience of AG *versus* surgical ablation and Dr. Harvey will present AG *versus* hypophysectomy data. With medical therapy, we can achieve the same results as surgical therapy. Our strong feeling is that we should no longer be doing ablative surgery. In the discussion session afterward, I will certainly look for some responses from people, such as Dr. Pearson, who are still supporting the surgical ablative procedures. A second problem we are facing is that we have too many therapies that appear to be relatively equal in their efficacy. I think we need more comparative trials. We have adopted TAM without any large prospective, comparative trials between TAM and DES or between TAM and Halotestin.

Dr. Bloom: This question is directed to both Dr. Harris and Dr. Lipton. One of the differences you pointed out, Dr. Lipton, in your study was that the response rate was a little better, 38%, and seemed to be more so in your receptor-positive patients, and you were actually trying select patients who were receptor positive; whereas in the English experience it seems to be just a straight, across-the-board presentation without any consideration being given to receptor status. Therefore, your data, the English experience demonstrating a 30% response rate, are what one would expect with hormonal therapy as it has been for essentially the last 100 years. The question I address to both of these investigators is, at this point in time do you think trials should continue in which receptor data are not available on patients? Because you really are going to be administering a therapy to a large group of patients who are not going to benefit from it, and as your survival curve showed in the people who do not respond, they are dying very rapidly because during an interval of time you may not be treating them appropriately.

Dr. Harris: I think the advent of these 2 therapies has to some extent superseded the need to know the receptor status. We have TAM and AG and we do not need to do hypophysectomy or adrenalectomy. We can give treatment easily which is well tolerated without very many side effects. Since a positive estrogen receptor may give a 50-50 chance of responding, you cannot rely on estrogen receptor status anyway if you are going to have to make the decision on rapidly progressive disease. So we make the decision clinically, because you need to do that. If it is not rapidly progressive disease, you are still only going to have a 50-50 chance of responding with positive receptor, and a 14% chance of responding with negative receptor, providing you believe your laboratory. I think there is a lot of interlaboratory variation and poor quality control between laboratories, and only a few centers probably do the assays reliably so that you know that a receptor-negative patient really is a receptor-negative patient.

Dr. Lipton: I think receptors ought to be part of the classification of patients in any study.

Dr. Bloom: I have had the good fortune of always being associated with a laboratory where the receptor determinations were excellent. You can get a high degree of predictability of the response to hormonal therapy with the receptor determinations. As a surgeon who has done a lot of adrenalectomies, given them up in anybody who is receptor negative, and now will probably never do adrenalectomies again because of the advent of these other drugs, I think many of us have come to the realization that it is inappropriate to treat patients with a hormonal agent when you have this type of information readily available from a good center. To say that it does not affect the patients is really contradicted in your own data in which you showed that of the patients who did not respond, many were dying within 4 or 5 months, which is the time period that you were caring for them in your trial. I am not going to overemphasize it, but the effect of chemotherapeutic agents in that group of patients is that you can prolong their survival as well as the ones that are going to respond hormonally. I only bring this up because it concerns me as a clinician that a large number of patients may not be getting appropriate therapy in an attempt to increase numbers in this type of study.

Dr. Harris: Let me answer that. Of the patients who did not respond to hormonal therapies, all of these women received Adriamycin and a combination chemotherapy regimen. Our policy for all of these trials has been that we tend to treat patients who do not have rapidly progressive lymphangitic or other rapidly progressive disease with hormones. Those who require chemotherapy regardless, we treat with chemotherapy. Those who fail to respond to the endocrine therapy go on to chemotherapy with Adriamycin, vincristine, and/or Adriamycin-vindesine. All patients who died after endocrine therapy were receiving chemotherapy.

Dr. McGuire: I think we are getting into a philosophical discussion here. Obviously, we have one proponent who would just like to add more drugs empirically and if he can pick up another 10 or 15% by adding another drug, that is great—as long as the toxicity is not too bad and the cost is not prohibitive. That is an oversimplification and perhaps too harsh an assessment of Dr. Harris' view. Then there is the other group, represented by Dr. Bloom and Dr. Lipton, who like to have as much information as possible to guide them in what they are doing. I think people in the audience can decide to which group they belong.

Dr. Troner: How fast can you see a response in nonosseous metastases, and do you think it appropriate that evaluation in nonosseous metastases be moved up, perhaps to 4 weeks instead of the 8 or 12 weeks?

Dr. Murray: Yes, we evaluated it at 3 months, but if there was obvious progression before that time then the patient was removed from the study and classified as a nonresponder. If she had undisputedly progressing disease, we did not wait the full 3 months.

Dr. Harris: Of course, it follows that anyone who met the usual criteria for progression was withdrawn from the study and went over to chemotherapy or the other arm of endocrine therapy, depending on at what stage she was in the study on the controlled trial.

Dr. Troner: I am not interested in progression; I am interested in response, rapidity of response. What is the fastest response you have seen in patients with cutaneous, pulmonary, or hematogenous metastases?

Dr. Harris: The fastest was within 2 to 3 weeks, but there is a gradual accumulation over the 3-month period, and there are people spotted throughout that period who are beginning to show an objective response—so within a month, certainly. But you continue to accumulate people and there has been work showing that even after 10 or 48 months you can see objective response; it can be very drawn out and you have to have sufficient observation time.

Dr. Paridaens: We had 44 patients treated with AG and 17 of them entered into objective remission. The time to achieve objective remission ranged from 15 to 240 days. The median time was about 3 months. We had a lot of patients who were classified as no change at 3 months but went into remission later.

Dr. Powles: This slide[2] shows by site, on 3 types of endocrine therapy with 100 patients, the time taken to achieve partial response and complete response. It is 15 weeks for soft tissue for partial response and 17 weeks for complete response; that is the median time. So half the patients went on to achieve partial remission as defined by the UICC criteria, after 15 weeks. We cannot stop at 3 or 6 weeks. These patients may go up to 45 weeks here and 49 weeks to achieve complete response. To achieve objective remission in bone, the median time was 41 weeks. So, really, it is nonsense to do an assessment at 6 weeks for objective response in bone.

[2] Slide not included.