

Estimated Potency of Casodex: A Problematic Design

TO THE EDITOR:

Given today's knowledge, when considering the choice of therapy for advanced prostate cancer, one should remember that the only treatment regimens demonstrated in randomized and placebo-controlled clinical trials to prolong life are the combination of Eulexin (flutamide) or Anandron (nilutamide) with a luteinizing hormone-releasing hormone (LHRH) agonist or orchiectomy, administered continuously until disease progression.¹⁻⁴

Although it is reasonable to attempt to improve upon the tolerability profile of endocrine therapy for prostate cancer, such changes should not be done at the expense of proven survival. This issue is particularly timely when considering the results presented by Schellhammer *et al.*^{5,6} comparing the 50-mg daily dose of Casodex (bicalutamide) with Eulexin (750 mg/day) for advanced prostate cancer. The choice of the low 50-mg dose of Casodex is apparently based on an overestimation of the potency of Casodex derived from an inappropriate animal model.^{7,8}

According to Schellhammer *et al.*,⁵ "on the basis of evidence from animal and pharmacokinetic and pharmacodynamic studies, the 50-mg daily dose of Casodex is likely to be as effective as the 750-mg daily dose of flutamide." However, the intact rat model is an inappropriate one in which to conduct comparative studies of pure antiandrogens because of the unreliable dynamic state of the hypothalamo-pituitary-testicular axis in such animals compared with men.

A true assessment of the biologic activity of antiandrogens in vivo requires animal models wherein the circulating levels of androgens are well controlled. Unfortunately, the data comparing Eulexin and Casodex in intact rats⁷⁻¹⁰ have no relevance to human males. The potent stimulation of luteinizing hormone and testosterone secretion in the intact rat by Eulexin is a biologic curiosity limited to the rat. Using that model, Furr *et al.*⁷ overestimated the potency of Casodex by failing to account for much higher serum testosterone levels in rats dosed with Eulexin. This miscalculation of the estimated potency for Casodex apparently explains the choice of the too-low 50-mg dose.¹¹

The most reliable data indicate that the true potency of Casodex is, at best, one third that of Eulexin,^{12,13} whereas the use of the intact rat model led to the suggestion that Casodex was 5 to 10 times more potent than Eulexin.⁷⁻¹⁰ It is worth noting that although early reports⁸ suggested that 50 mg/day of Casodex was equivalent to castration, it has been demonstrated by Chodak *et al.*¹⁴ that Casodex (50 mg/day) monotherapy was inferior to castration in terms of both survival and time to disease progression ($P \leq 0.002$). Survival was 3 months shorter in the group of patients who had received Casodex ($P < 0.0001$).¹¹ To our knowledge, this is only the second time that a treatment for prostate cancer has led to a survival shorter than the one routinely achieved by castration. The only other study that showed such a poor result was the one using medroxyprogesterone acetate,¹⁵ a compound known to have highly significant androgenic instead of antiandrogenic activity. Following those results, the use of medroxyprogesterone for the treatment of prostate cancer was quickly

abandoned. Soloway *et al.*¹⁶ also observed that although Casodex was well tolerated at a dose of 50 mg/day, it appeared to have suboptimal effects, thus suggesting the need for additional trials to evaluate higher doses. In contrast, a single-agent study using Eulexin (750 mg/day) has shown efficacy superior to diethylstilbestrol, which formed the basis for the choice of dose of Eulexin for combination therapy trials.¹⁷ The question arises whether a lower dose, or a once-daily dose (500 mg q.d.) of Eulexin is as effective in combination therapy as the current 750-mg dose. Current trials are underway to answer this question.

The choice of a 50-mg daily dose of Casodex by Schellhammer *et al.*⁵ was also based on the observation that "the 50 mg daily dose was well tolerated in patients with advanced prostate cancer." With that parameter in mind, the study protocol was designed to evaluate the difference between the two drugs by creating a hybrid efficacy-tolerability end point, namely, time to treatment failure (TTF).

Rather than the traditional measures of effectiveness used in prostate cancer trials (for example, median survival, median time to disease progression, best response achieved, duration of response), the use of TTF as the primary end point automatically enables one to overstate the importance of tolerability versus effectiveness. In fact, "treatment failure" was defined in Schellhammer *et al.*⁵ as "any of the following: adverse event leading to withdrawal of randomized therapy, objective progression, death, or withdrawal from the study for any reason, such as the patient's willingness to continue or an investigator's decision to remove a patient from the study." Given the choice of treatment failure instead of direct efficacy, a therapeutically more effective drug that causes additional (even minimal) side effects could appear less effective than a well-tolerated drug having less effect on tumor remission.

While the early reports suggested that the only significant tolerability difference between Casodex and Eulexin was the incidence of diarrhea, it may be relevant to mention the study questionnaire specifically asked patients about this side effect. At 49 weeks, 24% of patients taking Eulexin had reported diarrhea, and 25 patients in the Eulexin group were allowed to discontinue therapy (and were classified as treatment failures) due to diarrhea alone, versus only 2 patients taking Casodex. As a result, as early as 49 weeks, 13.7% more patients were treated in the Casodex arm due to diarrhea-associated treatment "failure," thus illustrating the serious bias introduced using this subjective end point.⁵

When the objective of a therapy is to prolong life, the use of a highly subjective efficacy end point such as TTF compromises any evaluation of efficacy, because it masks the true benefits of the drug on survival. In our experience with 2000 patients, as well as the 300 patients in the Intergroup NCI study,¹ no patient had to discontinue Eulexin therapy because of diarrhea.

Because it was known before the start of the Schellhammer study that diarrhea was more frequent with Eulexin, it is incorrect to say that "there was no bias to withdraw flutamide-treated patients because of diarrhea" or that "the double-blind randomization ensured balance of bias between the two arms."¹⁸ Blinding of a study does not eliminate a significant bias known to exist before treatment. The choice of treatment failure as primary end point thus

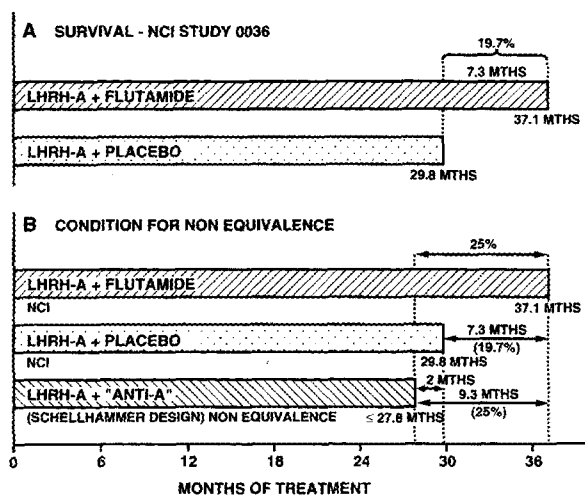


FIGURE 1. Illustration of the difference required to reject the null hypothesis that Casodex plus luteinizing hormone-releasing hormone (LHRH) agonist therapy is at least 25% worse than flutamide plus LHRH agonist (Schellhammer et al.'s criteria^{5,6}), using the survival data of the Intergroup NCI study¹ as reference (A). Because flutamide provides a 19.7% difference in survival (7.3 months), it can be seen that the Schellhammer et al. study does automatically provide a positive result, even in the absence of any therapeutic effect of Casodex because it would require Casodex to be worse than placebo to reach a 9.3-month or 25% difference compared to flutamide plus LHRH agonist (B). In fact, the use of a placebo (instead of Casodex in the Casodex arm) would give a positive result (without side effects).

introduced an important bias in favor of Casodex, one that could not be corrected by randomization.

The observation that patients given Eulexin were 34% more likely to "fail" treatment in the first 49 weeks clearly shows the degree of bias inherent in the design of Schellhammer et al.⁵ However, despite the fact that many more patients were untreated in the Eulexin group, survival at 95 weeks became identical in the two groups.⁶ Moreover, the significant difference in TTF between Eulexin and Casodex at 49 weeks (53% versus 42%, $P = 0.005$)⁵ had disappeared at 95 weeks (72% versus 68%, $P = NS$).⁶ Because similar results were obtained with Eulexin and Casodex at 95 weeks despite the fact that 29.8% more Eulexin patients were untreated, one could interpret these findings as indicating that Eulexin is sufficiently more effective than Casodex to compensate for the untreated patients in this group. Another possible interpretation is that many Casodex patients dropped off therapy between 49 and 95 weeks due to side effects other than diarrhea.

Assuming that the study design biases described above could be corrected by censoring all patients who stopped treatment for reasons other than disease progression or death, there remains one other unsolvable problem in Schellhammer et al.'s⁵ study: the requirement that Casodex be shown to be 25% worse than Eulexin to reject the null hypothesis that the two drugs are equivalent. Because the addition of Eulexin provides a 19.7% advantage over the LHRH agonist alone according to the Intergroup Study,¹

the 25% difference required in the Schellhammer et al. study is of greater magnitude than the effect achieved by Eulexin itself (Fig. 1). With such a design, the use of a placebo in place of Casodex would also yield a positive conclusion. In fact, to reject the null hypothesis, Casodex would have to decrease by 2 months the survival achieved with the LHRH agonist alone, thus illustrating that this study can only lead to a positive conclusion and could never show that Casodex is different from Eulexin.

The objective of total androgen blockade is to exert maximal inhibition of cancer cell proliferation and induce maximal apoptosis or cancer cell death. Because the 50-mg dose of Casodex was chosen based on a large overestimation of the drug's potency from preclinical studies,⁷⁻¹⁰ priority should be given to determining the therapeutically effective dose of this antiandrogen. Unfortunately, due to serious design biases, this information cannot be obtained from Schellhammer et al.^{5,6} or from any other Casodex study reported thus far. Until that issue has been resolved, the only treatments demonstrated to prolong life for patients with advanced prostate cancer are Eulexin or nilutamide in combination with an LHRH agonist or orchiectomy.

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