LETTER TO THE EDITOR

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Re: A review of continuous vs intermittent androgen deprivation therapy: Redefining the gold standard in the treatment of advanced prostate cancer. Myths, facts and new data on a "perpetual dispute"

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To the editor,

After mature randomized clinical trial, some criticisms on what we expect from intermittent androgen deprivation and how we have to administer IAD are still open. An extensive discussion on testosterone as ruler for retreatment should be opened.

I read the review by Zisis Kratiras et al. (1) with great interest and expectancy because intermittent androgen-deprivation (IAD) therapy, which is commonly used, is still in the 'empirical' stage. After many randomized clinical trials, who is the best candidates to IAD, what we expect from IAD and how we should administer IAD remain unknown.

Androgen-deprivation therapy (ADT) for the treatment of prostate cancer is old and it is based on the reduction of androgen hormones to a castration level. To effectively evaluate the response to surgical or chemical castration, we have to measure testosterone levels, which is the key point of the definition of castration-resistant prostate cancer.

The definition and strategy of IAD is to alternate androgen blockade (on-phases) with treatment cessation (off-phases), which allows for androgen recovery between treatment periods. The relevant clinical trials are summarized in the excellent review of Zisis Kratiras (1), as well as recently by Sciarra et al. (2).

The hypothetical value of IAD comes from the original experiment of Akakura et al. (3), which hypothesized and demonstrated in vivo that the replacement of androgens at the end of a period of castration-induced, apoptotic regression might result in the regeneration of differentiated tumor cells with further apoptotic potential.

Consequently, we expect that testosterone levels are the primary consideration of all clinical trials, but this is not always the case.

Laurence Klotz (4) and Gustavo Franco Carvalhal in his editorial comment to current paper correctly poses some questions. The review paper (1) shows that the induction periods and the criteria for resuming treatment are extremely variable and that both are PSA-driven. The selection criteria for IAD was a variable reduction with respect to the baseline PSA levels, but it is not clear whether the inadequate drop in PSA levels was linked to the primary extent of disease or

the incomplete response to hormonal therapy (testosterone > 20 ng/mL). Additionally, because the rationale of the 'off' phase is to permit testosterone recovery, a hypothetical trigger for retreatment should be the recovery of baseline testosterone, independent of the PSA levels. Moreover, testosterone recovery translates to a longer off phase and better quality of life.

Conversely, the recovery of the baseline testosterone level is the mainstay of IAD, which is otherwise an 'intermittent drug administration'. Because a significant percentage of subjects in IAD studies did not recover to the baseline testosterone levels (5) and suddenly received active retreatment, many patients had to be considered as receiving continuous androgen deprivation therapy. Upon analyzing all trials, no study has verified the impact of testosterone recovery with a more complex analysis with respect to the primary endpoint.

Based on these key points, I suggest that in guidelines to IAD patients should have PSA and testosterone levels assayed at baseline and every 3 months during the ON and off-treatment interval. Moreover, I think that we need to discuss the use of testosterone levels as trigger point for retreatment.

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