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Intermittent Androgen Deprivation Therapy: Conventional Wisdom versus Evidence

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Intermittent androgen deprivation (IAD) is one of the most interesting topics in the treatment of advanced prostate cancer (PCa). IAD is also a perfect example of how conventional wisdom can take over evidence-based medicine: IAD was acknowledged by the European Association of Urology guidelines not because of a high level of evidence but because the treatment “is at present widely offered to patients with [PCa] in various clinical settings” [1]. This decision defines *conventional wisdom*, a term coined in 1958 by Galbraith, as, “the ideas which are esteemed at any time for their acceptability” [2]. The author, however, already pointed out that there may be important differences between what is acceptable (the territory of the conventional wisdom) and what is true [2].

This situation is clearly illustrated by the publication in this issue of *European Urology* of the results of the pivotal phase 3 trial conducted by Calais da Silva et al on behalf of the South European Urological Group (SEUG) [3]. The trial compares IAD and continuous androgen deprivation in 766 patients, and although it bears some methodologic imperfections and bias, the trial is one of the first to reach full maturity, with a median follow-up of 51 mo [3].

An in depth lecture of the manuscript suggests that we have to revise our expectations regarding the impact of IAD on the behaviour of PCa. It is worth remembering that the rationale for using IAD comes

from a set of very elegant studies conducted by Akakura et al in animals in the early 1990s [4]. The concept was simple: a Shianogi mammary androgen-dependent cell line was grown sequentially in normal rats that were subsequently castrated so that tumour would be exposed intermittently to androgens. The concept was very promising, since the *in vitro* model indicated that IAD prolonged the duration of androgen dependence. This generated the stimulating hypothesis that IAD would act similarly in patients by delaying the onset of castration-resistant PCa and its associated debilitating and deathly complications. This initial observation was indeed followed by a series of phase 2 clinical trials that demonstrated IAD's feasibility [5].

The trial by Calais da Silva et al [3] does not confirm this historical hypothesis. Overall, the study was unable to detect any significant difference in overall survival (hazard ratio [HR]: 0.99; $p = 0.84$). Even more, an increase in the number of progressions in the IAD (127 in the intermittent arm and 107 in the continuous arm) is reported, the time to progression being even slightly longer in the continuous arm (HR: 0.81; $p = 0.11$). These findings are exactly the opposite of what we expected, based on Akakura's [4] experiment. Looking at the cause of death, we realise that Calais da Silva et al report a 10% increase in PCa death in the IAD group (23.6% in the IAD group vs 20.8% in the continuous group). Overall survival remains unaffected because there is an increase in death

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from cardiovascular disease and other causes in the continuous arm. It is very small number, but it allows us to formulate an alternative hypothesis that, in fact, IAD may be inferior to continuous androgen-deprivation therapy (ADT) once we have tackled IAD's cardiovascular and other toxicities.

Conventional wisdom asserts that IAD will help to alleviate side-effects during off-treatment periods, when testosterone comes back to normal, and to reduce the long-term comorbidities from ADT such as cardiovascular disease and accelerated bone loss. Several phase 2 studies have addressed these issues and validated the hypothesis [6,7]. The SEUG phase 3 trial confirms that hot flushes and sexual activity improved during therapy, although we must recognise that the study was not placebo controlled; thus, a placebo effect cannot be ruled out for the patients randomised in the intermittent arm since they are expecting doing better when ADT is suspended. In contrast, no significant effect was detected using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire, which assesses various domains of well being and general health. Once again, we may have to lower our expectations of the real benefit of IAD.

Finally, the SEUG trial highlights the important fact that IAD is not for every patient who needs ADT. First, only 81% of patients achieved a prostate-specific antigen (PSA) level >4 ng/ml after 3 mo of ADT and were effectively randomised in the trial—a proportion similar to the 85% of patients randomised in the Southwest Oncology Group (SWOG) 9346 trial after 7 mo of therapy [8]. Additionally, these two trials have demonstrated that the value of the nadir PSA after the induction was a strong predictor of final outcome. In the SWOG trial, patients with PSA of ≤ 0.2 ng/ml had less than one-fifth the risk of death of patients with PSA of >4 ng/ml ($p < 0.001$) and had significantly better survival than those with PSA between 0.2 and 4 ng/ml ($p < 0.001$). In the SEUG trial, both metastatic status and PSA level were independent predictors of progression, with distant metastasis and PSA level ≥ 4 ng/ml after induction being associated with a greater risk of progression. These predictive factors are confirmed in the Finn-Prostate Study VII [9]. ADT was administered for 6 mo, and 36% of patients did not meet the criteria for randomisation (ie, PSA < 10 ng/ml). These patients were primarily those with high PSA, elevated alkaline phosphatase, T4 tumours, poorly differentiated cancers, and extended metastatic disease [9]. These data help to draw the portrait of the ideal candidate for IAD: a patient with a moderately elevated PSA and a relatively low burden of disease, preferably nonmetastatic. Interestingly, these are also the patients in whom hormone therapy

can be delayed for several years without affecting survival or who can be treated with antiandrogens to avoid side-effects of castration. In EORTC trial 30891, 985 patients who were unfit for radical therapy were randomly assigned to receive immediate ADT or were deferred until symptomatic disease progression [10]. If overall survival was modestly increased in patients receiving immediate ADT (HR: 1.25, $p > 0.1$), it resulted from fewer deaths from non-PCa-related causes. Neither the time from randomisation to progression of hormone-refractory disease nor PCa-specific survival differed significantly. The more interesting message, however, was that the median time to start deferred treatment after study entry was 7 yr and that 26% of patients in the delayed ADT group died without ever needing treatment to be safely delayed [10].

Taken together, these observations counter the conventional wisdom that we are giving too many hormones and that IAD should be considered as standard therapy in PCa. We may advocate that we are giving ADT to too many patients and that IAD, instead of being an alternative to continuous ADT, is an alternative to surveillance in many patients with low to moderate tumour burden. Additionally, IAD will never be a “one size fits all” treatment, surely not in high-burden cancer, for those who really deserve ADT. Clearly, more phase 3 trials are needed to confirm that IAD does not jeopardise the effect on PCa mortality. In the meantime, we should only offer IAD in selected, well-informed cases and surely not acknowledge it as standard treatment in all patients.

Conflicts of interest: Bertrand Tombal is a consultant for Astellas, Ferring, and Astra-Zeneca.

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