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## Preface

This book brings important news in the field of prostate cancer: *androgen blockade is now recognized as a potential cure for localized prostate cancer and is no more considered as only palliative*, a characteristic essentially based upon observations made in metastatic disease.

The main objective of physicians managing patients with cancer is to permanently free them from the disease. It is thus a major progress to see that androgen blockade is now increasingly recognized as curative, conditional to its use in localized (when it is curable) instead of advanced and metastatic (when it has become non curable) disease. This news is particularly timely since more than 95% of patients can now be diagnosed by simple PSA screening and treated at the localized and potentially curable stage<sup>1</sup>, thus providing an explanation for the 33% decrease in prostate cancer deaths observed during the last fifteen years in the USA.

This extremely long delay in recognizing the curative potency of androgen blockade can be explained by two errors concerning androgen blockade which are still widespread. These errors, as indicated by Professor Akaza in this book, are still transmitted in the official guidelines of some urological associations as instructions to their members for use in their clinical practice. These two common errors are:

1. Application to localized prostate cancer of observations made in advanced disease. As well indicated in this book by Professors Akaza and Namiki, the temporary efficacy of androgen blockade due to the development of resistance to treatment is a characteristic typical of advanced and metastatic disease. There have never been valid reasons to apply to localized prostate cancer these observations of resistance to treatment made in advanced disease. In fact, contrary to the situation in metastatic prostate cancer, a continuous and very long term positive response with the high probability of a cure is observed in localized disease (chapters of Akaza and Namiki)<sup>2</sup> when proper (combined) androgen blockade is used. This possibility of cure is however conditional to the administration of combined androgen blockade started sufficiently early at the time of diagnosis.<sup>2</sup>  
The conclusion that androgen blockade is curative has been reached in many studies including a meta-analysis of the controlled clinical trials performed as adjuvant hormonal treatment in non-metastatic prostate cancer.<sup>3</sup> The author has concluded that androgen blockade given as adjuvant to surgery or radiotherapy should be classified as a treatment of curative intent for patients with poor prognosis non-metastatic prostate cancer. It should be clearly indicated that such positive results could even be recognized using a non optimal androgen blockade, namely monotherapy, while much better results are achieved with combined androgen blockade.

2. A second error is the extremely common use of monotherapy, a treatment much inferior to combined androgen blockade. A significant rate of cure (33%) can be reached with monotherapy in localized prostate cancer.<sup>4</sup> However, a major limitation of monotherapy (castration alone or an antiandrogen alone) is that 25% to 50% of active androgens are left in the prostate under monotherapy (see chapters by Nishiyama et al and Mostaghel and Nelson).<sup>5,6</sup> These androgens made locally in the prostate continue to stimulate prostate cancer after any treatment limited to castration or an antiandrogen alone, thus permitting continued stimulation of cancer proliferation and metastasis at distance where resistance to treatment develops and cure becomes impossible.

The simple addition of a pure antiandrogen to castration in order to block the action of the androgens made locally in the prostate increases the potential of cure from 33% with monotherapy<sup>3,4</sup> to more than 90% with combined therapy.<sup>2,6</sup> It is very important to read Professor Akaza in this book saying: "cure of prostate cancer is almost always possible with current androgen blockade....".

Discovery of the local formation of androgens from DHEA of adrenal origin by the action of the enzymes of intracrinology<sup>7,8</sup> has indicated the need to develop combined androgen blockade<sup>5</sup> which simply adds to castration (medical or surgical) a pure antiandrogen in order to block the action of the androgens made locally in the prostate. As illustrated in the chapters of Luu-The et al. and Pelletier, all the enzymes required to make androgens from DHEA are expressed in the prostate.

The observation of extremely low levels of testosterone in the blood after castration (5% of intact men) in the presence of a 25–50% intraprostatic concentration of dihydrotestosterone compared to untreated men is explained by the local metabolism of the active androgens into inactive glucuronides which are released from the prostate and other target tissues in the blood (see chapter of Barbier and Bélanger), while the active androgens testosterone and dihydrotestosterone do not diffuse out of the cells in significant quantities and are only seen in minute quantities in the blood, giving the illusion that tissue androgens are similarly low.

The recently available data show that combined androgen blockade is very efficient, not only in the treatment of truly localized disease which can be cured in almost all cases but that the same treatment could also be efficient in the prevention of prostate cancer by inhibiting PIN (Prostate Intraepithelial Neoplasia) lesions (see chapters by Hull and Bostwick and by Têtu). A detailed description of the morphological changes induced by combined androgen blockade in prostate cancer is presented in the chapter of Têtu.

Knowing the extremely high sensitivity of prostate cancer to androgens, a logical approach for prevention of the disease is inhibition of androgen formation or action. Particularly important studies have been performed with the 5 $\alpha$ -reductase inhibitors finasteride and dutasteride (see chapter by Rittmaster).

Clearly, combined androgen blockade applied at the localized stage can cure most of the patients and androgen blockade should no more be considered as palliative but instead as a curative treatment which needs to be applied at the localized stage in order to take advantage of its extremely high level of efficacy. With today's knowledge, one should benefit from the possibility of diagnosis of prostate cancer at the localized stage in more than 95% of cases by simple screening with PSA<sup>1</sup>, thus avoiding metastatic and non curable disease. For the patients suffering from metastatic disease, combination therapy is the treatment of choice and the only one shown to prolong life<sup>5,6</sup> (see chapters by Klotz and Msaouel et al.). Efficient blockade of the androgen receptor

can even play a role in patients who failed primary androgen blockade (see chapters by Mohler and McPhaul).

Starting combined androgen blockade at the localized stage at time of diagnosis is the only way to markedly decrease deaths from prostate cancer as it is well described in the chapters of Akaza, Namiki and Maroni.<sup>2,6</sup> This approach has the potential to practically eliminate deaths from prostate cancer if the proper treatment (combined androgen blockade) is applied early at time of diagnosis and metastasis to distant sites is avoided.<sup>6</sup> Prostate cancer death can now be an exception if today's medical knowledge is correctly and timely applied in clinical practice.<sup>6</sup>

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