

CAN COMBINED ANDROGEN BLOCKADE PROVIDE LONG-TERM CONTROL OR POSSIBLE CURE OF LOCALIZED PROSTATE CANCER?

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ABSTRACT

Objectives. To investigate the possibility that more complete blockade of androgens or combined androgen blockade (CAB) could lead to even longer term control of localized prostate cancer. A series of recent studies have shown important benefits on survival using medical or surgical castration in localized or locally advanced prostate cancer.

Methods. The effect of CAB on long-term control or possible cure of prostate cancer was evaluated by the absence of biochemical failure or prostate-specific antigen (PSA) rise for at least 5 years after cessation of continuous treatment. A total of 57 patients with localized or locally advanced disease received CAB for periods ranging from 1 to 11 years. Twenty patients with Stage B2/T2 prostate cancer who were treated for a median duration of 7.2 years (range 2.8 to 11.7) with CAB stopped treatment and were followed up for a median of 4.9 years. Eleven patients with Stage B2/T2 also received CAB but for only 1 year. Twenty-six patients with Stage C/T3 treated with continuous CAB for a median of 9.9 years (range 3.8 to 11.3) with undetectable PSA levels stopped treatment and were followed up for a median of 5.6 years. The median follow-up since diagnosis was 14.6 years for patients with Stage B2/T2 and 16.4 years for patients with Stage C/T3 disease.

Results. With a minimum of 5 years of follow-up after cessation of long-term CAB, two PSA rises occurred among 20 patients with Stage T2-T3 cancer who stopped treatment after continuous CAB for more than 6.5 years, for a nonfailure rate of 90%. For the 11 patients who had received CAB for 3.5 to 6.5 years, the nonfailure rate was only 36%. The serum PSA increased within 1 year in all 11 patients with Stage B2/T2 treated with CAB for only 1 year, thus indicating that active cancer remained present after short-term androgen blockade despite undetectable PSA levels. In all patients who had biochemical failure after stopping CAB, the serum PSA level rapidly decreased again to undetectable levels when CAB was restarted and remained at such low levels afterward. Of these patients, only 1 patient had died of prostate cancer at last follow-up.

Conclusions. The present data suggest that long-term and continuous CAB offers the possibility of long-term control or possible cure of localized prostate cancer. UROLOGY 60: 115-119, 2002. © 2002, Elsevier Science Inc.

The major source of controversy concerning the early diagnosis and treatment of prostate cancer has been that, until recently, no prospective

and randomized trial had shown statistically significant benefits on survival for the treatment of localized disease.^{1,2} Six prospective randomized trials have recently demonstrated that an important prolongation of life was observed in patients with localized prostate cancer treated with androgen blockade.³⁻⁸ At 5 years of follow-up, these studies showed improved cancer-specific survival rates ranging between 37% and 81%.

Although most studies performed to date of localized prostate cancer have used monotherapy (medical or surgical castration),³⁻⁸ there are good reasons to believe that even better results could be obtained with more complete or combined androgen blockade (CAB).⁹⁻¹⁴ Because we had already

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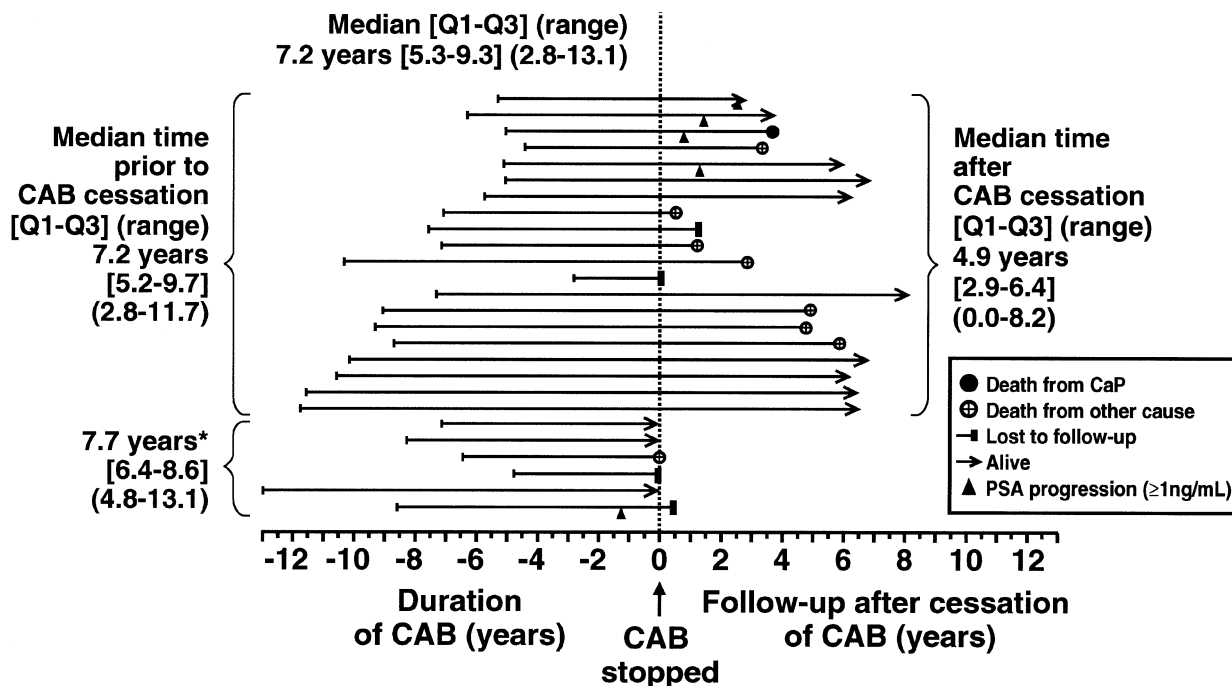


FIGURE 1. Duration of treatment with CAB in 26 patients with Stage B2/T2 disease and follow-up after cessation of CAB in 20 patients who had undetectable PSA levels for at least 4 years during continuous CAB treatment (median 7.2 years). Treatment was not stopped in the other 6 patients.

obtained evidence for the high efficacy of long-term and continuous CAB in localized prostate cancer,¹⁵ we believed it was important to examine the long-term outcome of these patients as assessed by biochemical failure or PSA rise after cessation of continuous CAB administered for periods of up to 11.3 years.

MATERIAL AND METHODS

Of 37 patients diagnosed with Stage B2/T2 prostate cancer who were willing to stop CAB, 26 received CAB alone for a median duration of 7.2 years (range 2.8 to 11.7) and 11 were treated for only 1 year. A cohort of 115 patients with Stage C/T3 disease also received continuous CAB, as described.¹⁶ Of these, 20 were treated for a median duration of 9.9 years (range 3.8 to 11.3) with undetectable PSA levels and were willing to stop CAB. The stage of the disease was established after analysis of the histopathologic specimens and detailed clinical, urologic, biologic (including prostatic and phosphatase) and/or PSA determination, and radiologic evaluation, as described.¹³ Patients were entered in the program after institutional review board approval and after signing an informed consent form.

Enrollment of patients began on January 15, 1988 and stopped on April 7, 1997, although the patients already entered continued to be followed up for PSA and survival. The patients who received androgen blockade alone were those who refused enrollment into other clinical trials using radical prostatectomy or external beam radiotherapy alone or in combination with hormonal therapy,^{17,18} or who were not candidates for surgery or radiotherapy. The endpoints were biochemical failure, clinical progression of disease, overall survival, and cancer-specific survival.

The patients received a combination of the luteinizing hor-

mone-releasing hormone (LHRH) agonist (D-Trp⁶, des-Gly-NH²₁₀) ethylamide (Deslorelin) and the pure antiandrogen flutamide. The LHRH agonist was injected subcutaneously at a daily dose of 500 μ g during the first month followed by 250 μ g every day thereafter. More recently, starting in 1993, patients received monthly injections of Zoladex or Lupron. The antiandrogen was started 1 day before the first administration of the LHRH agonist. Flutamide was given orally at a dose of 250 mg every 8 hours. At each follow-up visit, performed every 3 or 6 months, patients had a physical examination, including a digital rectal examination, basic biochemical assessment, and evaluation of serum prostatic acid phosphatase (PAP) and/or serum PSA. Radionuclide bone scan, chest radiograph, and skeletal radiographic assessment were performed when indicated. Biochemical failure was defined as the elevation of serum PSA greater than 1.0 ng/mL.

RESULTS

STAGE B2/T2

In 26 patients with clinically localized prostate cancer who received CAB with the antiandrogen flutamide and an LHRH agonist as the only treatment for as long as 11.7 years (median 7.2), the first, and so far only, progression of cancer as indicated by a rise of serum PSA occurred in 1 patient who had received CAB for 7 years and 4 months.

Because the serum PSA had remained undetectable for more than 4.0 years under continuous CAB treatment in 25 patients, CAB was stopped in 20 of them (Fig. 1). The median follow-up after cessation of treatment was 4.9 years (range 0.0 to 8.2). Progression or biochemical failure after cessation

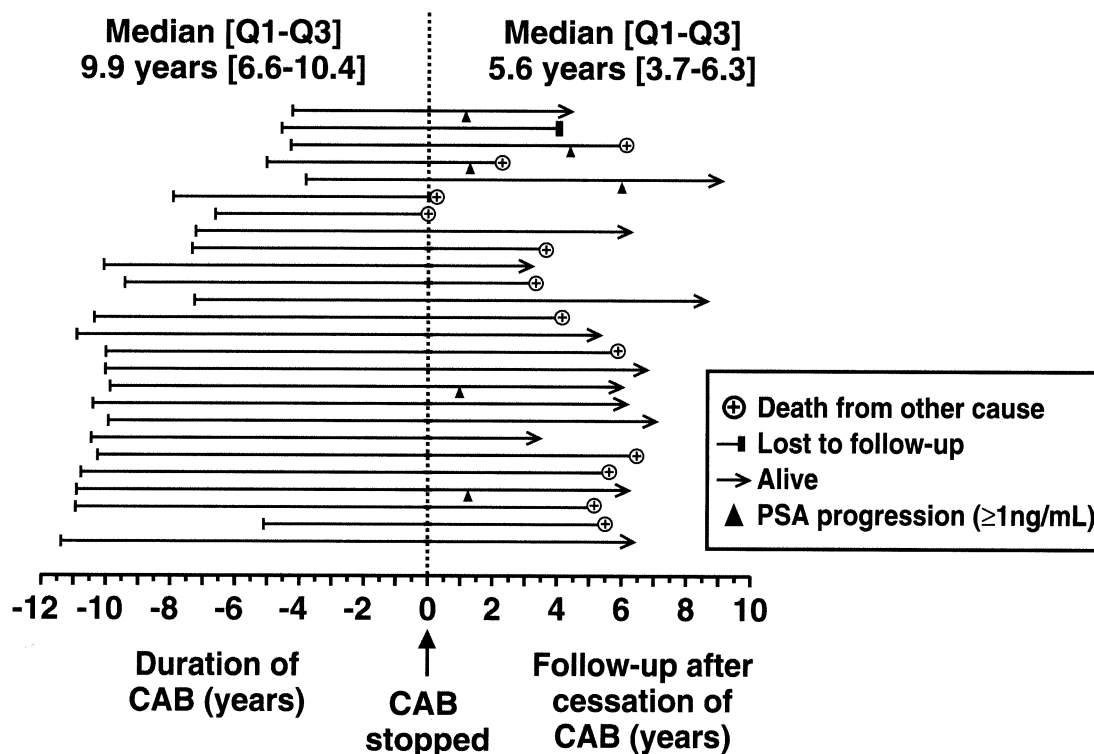


FIGURE 2. Duration of treatment with continuous CAB in 26 patients with Stage C/T3 prostate cancer who stopped treatment after a median of 9.9 years, with a median follow-up of 5.6 years after CAB cessation.

of CAB and as illustrated by a PSA rise has occurred in only 4 patients. The four PSA progressions occurred 0.7, 1.2, 1.4, and 2.6 years after the arrest of CAB in patients who had been treated with continuous CAB for 5.0, 5.1, 6.3, and 5.3 years, respectively. No progression occurred in the 12 men treated continuously for more than 6.5 years before treatment cessation, including 6 who had a follow-up of 5 years or more after treatment cessation (Fig. 1). Seven patients died of causes other than prostate cancer: one of lung cancer, four of cardiac disease, one of myelodysplastic syndrome, and one of colon cancer. One patient was lost to follow-up from the time of stopping CAB. Ten patients were alive with a low PSA after a median follow-up of 4.9 years after CAB cessation and a median survival of 14.6 years after starting CAB (Fig. 1).

STAGE C/T3

Twenty-six patients with Stage C or T3 prostate cancer at diagnosis had an undetectable serum PSA for a median duration of 9.9 years (range 3.8 to 11.3) while receiving continuous CAB. After stopping CAB, the serum PSA increased to greater than 1.0 ng/mL in only 6 of them (23%) during a median follow-up of 5.6 years (range 0 to 9.1) after stopping CAB (Fig. 2). The serum PSA thus remained undetectable in 20 patients (77%) for a median follow-up of 5.6 years. The 6 patients with a PSA

rise had received continuous CAB for 3.8, 4.2, 4.2, 5.0, 9.9, and 10.9 years before stopping treatment. In these 6 patients, the PSA rise (1.0 ng/mL or greater) occurred 6.0, 4.7, 1.1, 1.3, 1.0, and 1.3 years after stopping CAB. Among the 6 patients with a PSA rise after stopping continuous CAB, the PSA rise occurred within 1.5 years in 4 of them. In the patient who had a PSA rise 6.0 years after the arrest of CAB, the PSA level was at 14 ng/mL, but no PSA measurement had been performed during the 6 previous years, making it most likely that the PSA rise had occurred much earlier. Thirteen patients were still alive with a low PSA after a median follow-up of 5.6 years after CAB cessation and with a median survival of 16.4 years after first starting treatment with CAB (Fig. 2). No patient died of prostate cancer in this group. Eleven patients have died of causes other than prostate cancer.

When biochemical failure occurred after long-term and continuous CAB, it was observed in most cases within 1.5 years after CAB cessation. In fact, in 6 (60%) of the 10 cases, the PSA rise was observed within 1.5 years after CAB interruption. It is important to indicate, however, that the PSA decreased to undetectable levels in all patients who restarted CAB at the time of biochemical failure. The patients who continued to have an elevated PSA were only those who did not immediately restart CAB for various reasons or who used mono-

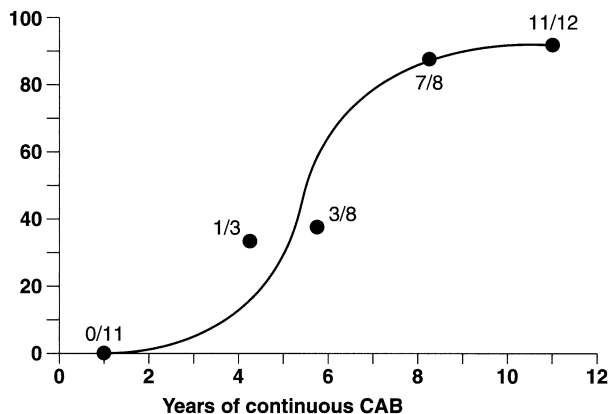


FIGURE 3. Effect of treatment duration of localized prostate cancer with continuous CAB on the probability of long-term control or cure of the disease as determined by no recurrence of PSA rise for at least 5 years after CAB cessation. Point at 4.75 years of treatment (33%) refers to 3 patients treated with CAB for 3.5 to 5.0 years and followed up for at least 5 years; point at 5.75 years refers to 8 patients treated continuously with CAB for 5.0 to 6.5 years before treatment cessation. Point at 8.25 years refers to 8 patients treated continuously for 6.5 to 9.0 years, and point at 11 years refers to 12 patients treated for 10 to 11.7 years with continuous CAB before stopping treatment. All patients were followed up for at least 5 years after continuous CAB or until PSA rise. Only 1 patient died of prostate cancer and 18 have died of other causes.

therapy, namely an LHRH agonist or orchiectomy alone, at the time of biochemical failure.

Much less positive results in terms of biochemical failure were observed, however, in patients who received CAB for only 1 year before stopping treatment. In fact, in this group of 11 patients treated with CAB for only 1 year, the serum PSA level increased in all within 1 year after stopping CAB, thus indicating that cancer had remained viable in all cases, despite an undetectable PSA.

It is of major interest to see how PSA failure inversely correlated with the duration of continuous CAB before treatment cessation. Of the 57 patients with Stage B2/T2 or C/T3 disease treated continuously with CAB for various intervals up to 11.7 years, only two PSA rises occurred in the 33 patients who had received CAB for more than 6.5 years before stopping treatment. When considering 5 years with no PSA rise after CAB cessation as the parameter of long-term control or possible cure of cancer, the no-failure rate was 90% (18 of 20) in this group of patients (Fig. 3). When looking in more detail at this group of patients, the no-failure rate was 87.5% (7 of 8) for patients previously treated with CAB for 6.5 to 10 years before stopping treatment and was 91.7% (11 of 12) for those previously treated for 10 to 11.7 years. The other

patients of this group treated for more than 6.5 years had the following outcomes: 9 deaths from causes other than prostate cancer, 1 patient lost to follow-up, and 2 patients with a follow-up shorter than 5 years but still with undetectable PSA levels.

On the other hand, for the 11 patients treated for 3.5 to 6.5 years with continuous CAB who had biochemical failure and who were followed up for at least 5 years with no PSA rise or who had biochemical failure before 5 years of follow-up, a PSA rise occurred in 7 cases, for a no-failure rate of only 36%. The nonfailure PSA rate at 5 years of follow-up after CAB cessation was 37.5% (3 of 8) for the 8 patients treated for 5.0 to 6.5 years; for those treated for 3.5 to 5.0 years, the nonfailure rate was 33.3% (1 of 3) (Fig. 3).

Among the patients who had a PSA rise on CAB cessation after more than 6.5 years of continuous treatment, no PSA rise was seen in patients originally diagnosed with Stage T2 disease; the only two biochemical failures were seen in patients diagnosed with Stage T3 disease or patients diagnosed with locally advanced disease. Despite these PSA rises after cessation of long-term and continuous CAB, a decrease of PSA to undetectable levels was observed in all cases when CAB was restarted, independent of the duration of the original CAB administration, indicating that the cancer remained androgen sensitive in all cases during long-term CAB.

COMMENT

The present data show that long-term and continuous treatment with CAB alone is highly efficient in controlling localized prostate cancer and that possible cure of the disease indicated by no rise of PSA for 5 years after stopping CAB can be achieved in most cases.

The results of the present study also indicate that when biochemical failure occurs after cessation of long-term and continuous CAB, the PSA rise occurs rapidly, usually within 1.5 years after treatment cessation. When 1.0 ng/mL was taken as the criterion of PSA progression, biochemical failure occurred earlier than 1.5 years after CAB cessation in 6 of 10 cases. Moreover, except for the 10 patients with a PSA rise greater than 1.0 ng/mL (biochemical failure) and the 4 patients in whom the PSA level increased significantly but did not reach 1.0 ng/mL, PSA remained undetectable after CAB cessation in all the other patients treated for more than 3 years. This finding strongly suggests that not only had the cancer disappeared or was inactive but that normal luminal prostatic cells, which are the source of PSA,¹⁹ had also disappeared by apoptosis or had remained nonfunctional after long-term CAB, despite CAB cessation for a long

period. Another most important observation made in the present study is that PSA rapidly returned to undetectable levels in all cases when CAB was administered at the time of biochemical failure after cessation of long-term and continuous CAB, indicating that the cancer remained androgen sensitive during long-term CAB.

On the basis of the above-described data, it can be estimated that a period of more than 6 years of continuous CAB is required to control localized prostate cancer efficiently. At approximately 6 years of treatment, long-term control or possible cure of cancer appears to be achieved in approximately 50% of cases. However, as shown in Figure 3, when CAB is continued longer, a much higher rate of success is achieved, with an approximately 90% cure rate at treatment durations ranging from 6.5 to 11.7 years. In clinical practice, one possibility is to stop treatment at 6 years, thus achieving the required long-term control of cancer in approximately 50% of cases. In the event of a PSA rise expected in the other 50% of patients, the same CAB should be re-administered without delay for another 3 years. A major mistake, starting with our own neoadjuvant trial started in 1988,¹⁷ has been that CAB has generally been administered for much too short a time.

With the knowledge of the above-described data, it seems reasonable to suggest that the minimal duration of continuous CAB should be 6 years, thus providing an approximately 50% probability of long-term control or possible cure of cancer. With a longer duration of CAB, the probability increases to about 90% at 8 to 10 years of treatment. The present data indicate that possible cure of the disease can be obtained in most patients with localized prostate cancer treated continuously with CAB for more than 6 years, thus raising hopes for the treatment of patients with failure after surgery, radiotherapy, or brachytherapy for whom no or minimally effective alternative therapeutic approaches exist. Such data clearly indicate the interest of a large-scale randomized study comparing monotherapy versus CAB in the group of patients with biochemical failure after first therapy with a curative intent. Care should be taken, however, to start treatment early after the PSA rise to use androgen blockade at its maximal level of efficacy, namely when the cancer is still localized to the prostate or the prostatic area and before metastases reach the bones when cure becomes the exception.

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