Practical aspects of hormonal therapy for localized prostate cancer

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In the past, hormonal therapy was only used for the treatment of metastatic prostatic cancer, but it has now assumed an increasingly important role in the management of intermediate and high risk localized prostate cancer as neoadjuvant or adjuvant treatment. It also has a role in treatment of local or distant failure after radiation. This review summarises the recent developments and the issues to be explored in the future: from chemoprevention to treatment. 5-alpha-reductase inhibition using drugs such as finasteride have been shown to decrease androgenic stimulation of the prostate and currently being tested in chemoprevention trials. Bilateral orchiectomy has been regarded as the gold standard of therapy, to which other treatments are compared. Most published studies showed no extra benefit of total androgen blockade (TAB) over monotherapy. TAB results in more hot flushes, fatigue, bone and joint pain, osteoporosis and fracture, anaemia, impotence. Anti-androgens do not seem to affect sexual function, physical capacity, strength and vitality as much. However gynaecomastia is more common with monotherapy antiandrogen than TAB. When hormone is combined with radiotherapy in both RTOG 85-31 and RTOG 86-10 studies, statistically significant improvements in outcome were observed between the radiotherapy and hormones combined (group I) and radiotherapy alone (group II) groups, when analysed for biochemical disease-free survival and distant metastases failure. Currently another ongoing research area is the intermittent androgen deprivation approach, which is meant to provide treatment to control the tumour, with a potential for prolonged therapy-free intervals resulting in improved quality of life, delay in progression to androgen independence, and reduced cost of therapy.

Terapia hormonalna w miejscowo zaawansowanym raku prostaty – aspekty praktyczne

Terapia hormonalna, jeszcze niedawno stosowana tylko w rozsianym raku prostaty, staje się obecnie coraz ważniejszym elementem leczenia zlokalizowanego raka prostaty u chorych, tak ze średnim, jak i z wysokim ryzykiem. Bywa stosowana zarówno jako leczenie adiuwantowe, jak i neoadiuwantowe, ma również istotne znaczenie w leczeniu wznów miejscowych lub przerzutów po radioterapii. Niniejsza praca poglądowa ma na celu podsumowanie dotychczasowych postępów leczenia hormonalnego oraz nakreślenie perspektyw jego dalszego rozwoju od chemoprewencji do leczenia.

Dowiedziono, że inhibitory 5-alfa-reduktazy, takie jak finasteryd, zmniejszają stymulację androgeniczną gruczołu krokowego. Są one obecnie poddawane ocenie w toku badań nad chemoprewencją. Jak dotychczas, za złoty standard w terapii hormonalnej uznawano obustronną orchidektomię – stanowi ona punkt odniesienia dla porównywania wyników innych form leczenia hormonalnego. Niektóre publikowane badania nie wykazały dodatkowych korzyści płynących z całkowitej blokady androgenowej (total androgen blockade – TAB), w porównaniu z monoterapią. Po całkowitej blokadzie androgenowej chorzy częściej skarżą się na uderzenia gorąca, znużenie, bóle kostno-stawowe, osteoporozę, złamania kości i impotencję. Wydaje się, że anty-androgeny nie wpływają w tak znacznym stopniu na aktywność seksualną, sprawność fizyczną, siłę i witalność. Z drugiej strony ginekomastia częściej towarzyszy monoterapii antyandrogenowej niż całkowitej blokadzie androgenowej. Badania przeprowadzone w celu oceny skuteczności leczenia obejmującego połączenie terapii hormonalnej z radioterapią (RTOG 85-31 i RTOG 86-10) wykazały znamienną statystycznie poprawę wyników leczenia w toku terapii łączonej, w porównaniu z leczeniem tylko radioterapią – oceniano wykładniki biochemiczne przeżycia bez choroby oraz niepowodzenia leczenia pod postacią odległych przerzutów. Inny kierunek badań obejmuje przejściowe pozbawienie chorego wpływu androgenów, co umożliwia ograniczenie choroby i stwarza możliwość wydłużenia przerw w terapii antyandrogenowej, a w efekcie poprawia jakość życia, odwleka moment całkowitej blokady androgenowej i zmniejsza koszty leczenia.

Key words: prostate cancer, hormone, radiotherapy, surgery
Słowa kluczowe: rak prostaty, hormony, radioterapia, chirurgia

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Role of hormonal manipulation for chemoprevention

5-alpha-reductase inhibition using drugs such as finasteride have been shown to decrease androgenic stimulation of the prostate. In clinical studies, 5-alpha-reductase inhibitors suppress serum and intraprostatic levels of dihydrotestosterone, an important promoter of prostate cancer, leading to reduction in prostate size and suppression of glandular cell activity as measured by PSA secretion [1]. In addition, 5-alpha-reductase inhibitors have demonstrated an excellent safety profile and tolerance in controlled clinical trials.

No significant metabolic effects have been observed in gonadotropin secretion, spermatogenesis, serum lipids or glucose tolerance. The efficacy and safety of 5-alpha-reductase inhibitors in studies to date, combined with the androgen dependence of tumour production, strongly supports investigating their use for chemoprevention of prostate cancer.

A SWOG clinical trial is underway using finasteride to assess this hypothesis: the Prostate Cancer Prevention Trial has completed randomisation of over 18,000 healthy men, aged 55 and older, to either finasteride (5 mg/day) or placebo to be taken for seven years [2]. The primary objective of this study is to determine whether finasteride can reduce the prevalence of prostate cancer over a seven-year period [3].

Apart from finasteride, epidemiological and laboratory studies also suggest that those with high selenium and vitamin E intake may lower the risk of prostate cancer [4].

Choice of hormone

Experience of hormonal therapy for adjuvant or salvage treatment is based on its effect on metastastic disease. Prostate cancer responds to androgen hormonal ablation with bilateral orchiectomy, an approach that is regarded as the *gold standard* of therapy but not always the preferred treatment of patients, due to psychological impact of disfigurement and irreversibility. Oestrogen therapy is an alternative but is associated with side effects, such as hot flushes and gynaecomastia, which frequently leads to treatment cessation. Luteinising hormone-releasing hormone (LHRH) analogues work by initially producing a surge of androgen, followed by a down-regulation in hormone production to effect a medical castration [5]. Various groups have studied the effects of androgen blockade administered as monotherapy and as combination therapy: LHRH analogue plus antiandrogen.

The National Cancer Institute intergroup protocol 0036, which is the largest cooperative study to date of patients with advanced prostatic cancer, showed that combination therapy with leuprolide and flutamide offered greater benefit in both time to disease progression and median survival while circumventing tumour flare and its associated symptoms [6, 7]. The subgroup of good performance status and minimal metastatic disease showed particularly benefit from the total androgen blockade versus leuprolide alone [8]. Thus, combination therapy for total androgen ablation becomes an important treatment option for adjuvant and salvage treatment. However, some may choose to use monotherapy due to expense, side effects and some published studies showing no extra benefit to total androgen blockade (TAB) [9-11].

In a study 220 patients with either locally advanced or disseminated prostate cancer were randomly assigned to treatment with bicalutamide 150 mg daily or the combination of flutamide 750 mg daily plus monthly goserelin acetate injections. At a median follow-up time of 38 months there was no difference in the duration of either progression-free survival or overall survival. Median time to progression was 25 months in the bicalutamide group and 23 months in the TAB group. Median survivals were 44 and 45 months respectively. Cancer specific mortality rates were also comparable [12].

In the past, flutamide was the most common monotherapy. Androcur (cyproterone acetate) was also commonly used and this works both on the periphery and central mechanism, so it is one form of TAB.

Nowadays more physicians are changing to use Casodex (bicalutamide) because it has fewer side effects and is less likely to cause hormone-resistance than flutamide. An interesting publication on Casodex mono-therapy showed that it is less effective than castration in patients with metastatic disease with a difference in median survival of six weeks [13]. However it has shown a benefit in terms of quality of life and subjective response when compared to castration and that it has an acceptable tolerance profile.

TAB results in more hot flushes, fatigue, bone and joint pain, osteoporosis, fracture, anaemia and impotence. Anti-androgens do not seem to affect sexual function, physical capacity, strength and vitality as much. However gynaecomastia is more common with monotherapy antiandrogen than TAB [14]. Diarrhoea, nausea and asthenia were also more common in patients treated with bicalutamide than in those treated with castration [14].

Among the different anti-androgens, flutamide tends to cause more gastrointestinal upset and liver toxicity. Nilutamide has a relatively high incidence of side effects, including decreased adaptation to darkness, interstitial pneumonitis, nausea, and alcohol intolerance. Bicalutamide has a very low incidence of above side effects [14].

Hormonal therapy as primary treatment

Although it is not commonly used in the United States, some patients in other countries may prefer this primary treatment because of its convenience. The disadvantage is that when the patient develops hormone resistance, it is very difficult to justify the rationale of prescribing this non-curative treatment.

The National Cancer Institute of Canada (NCIC PR.3) has joined the Medical Research Council (MRC) of United Kingdom in the INT T94-0110 trial. The trial is ongoing and evaluates any benefit from the addition of

radiation therapy to the treatment of patients with cancer of the prostate who are receiving TAB in terms of overall survival, time to progression, symptomatic local control and quality of life.

Figure 1 shows a patient with a locally extensive prostate cancer involving the bladder. Surprisingly he only had mild urinary obstruction that was successfully treated with transurethral resection. He declined radical radiotherapy and preferred to have hormonal treatment alone.
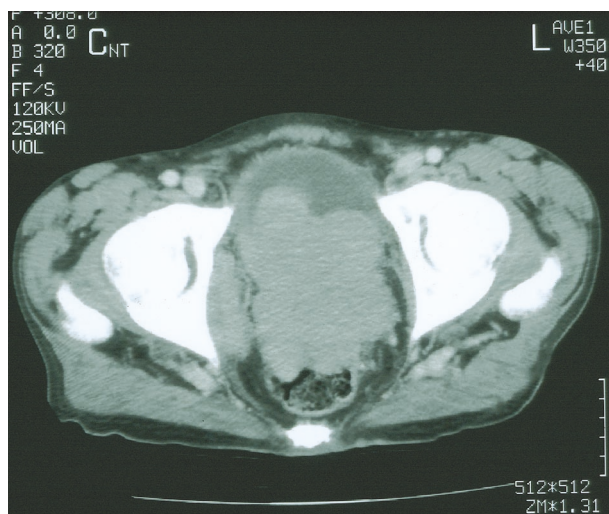

Figure 1. CT scan showing a locally extensive prostate cancer involving the bladder

Hormonal therapy combined with surgery

There are studies both for and against the approach of hormonal therapy combined with surgery. The Mayo Clinic studied 22 patients with clinical stage B2 (T2c) or C (T3) prostate cancer who underwent androgen deprivation therapy before radical prostatectomy as part of a down-staging protocol: group 1 cases [15]. The concentration of serum PSA was determined before and at the conclusion of androgen deprivation therapy, just before operation. For each group 1 patient a matched patient who had not received preoperative endocrine therapy was chosen: group 2 cases.

The ages of both group 1 and 2 patients were similar and the clinical stage of disease and pre-treatment tumour grade in group 2 were identical to the stage and grade in group 1. In addition, the serum PSA value in group 2 was similar to that of group 1 before initiation of androgen deprivation therapy. In group 1 the median serum PSA concentration was 14.8 ng/ml with a range of 3.1-99 ng/ml, before endocrine therapy and a median of 0.2 ng/ml with a range of 0.1-3.4 ng/ml, after hormonal treatment. Group 2 cases had a median level of 13.3 ng/ml and range of 3.4-100 ng/ml. The median decrease in the serum PSA concentration for group 1 as a result of androgen deprivation therapy was 98.5%. The radical prostatectomy specimens from these two groups of similar patients had no differences with regard to maximum

tumour dimension, pathological stage and deoxyribonucleic acid ploidy status. These findings indicate that serum PSA becomes an unreliable indicator of disease status after initiating pre-operative androgen deprivation therapy and that pre-operative androgen deprivation therapy has little or no benefit for decreasing the extent of tumour or pathological stage.

The observations in a different study showed more difficulties and the blood loss was higher in patients who had pre-operative hormonal deprivation [16]. This finding is the opposite to the experience from Quebec [17] where it was found that the volume of the prostate gland decreased by approximately 48% as assessed by TRUS and digital rectal examination after three months of flutamide and a LHRH agonist. The atrophy of the prostate gland markedly facilitated dissection of the prostate from closely associated and vulnerable structures such as the prostatic apex and the prostatic posterolateral neurovascular bundle. Impressive down-staging effects of the combination therapy on the histology of prostatic tumours were observed, including the absence of detectable cancer in 12/50 surgically removed prostate glands. The median time for recovery of potency after therapy was 7.5 months after cessation of the combination therapy.

Hormonal therapy combined with radiotherapy

RTOG 85-31 and RTOG 86-10 studies examined the questions of how long should hormonal therapy be given and who will benefit from it. Patients were randomised to receive long-term hormones (LTH) on RTOG 85-31 and received goserelin, continued indefinitely, but starting the last week of external beam radiotherapy. Patients treated with short-term hormones (STH) on RTOG 86-10 received goserelin and flutamide two months prior to and during radiotherapy. The median follow-up for all patients was 71 months with a range of 0.6-129 months.

Combining both studies, statistically significant improvements in outcome were observed between the radiotherapy and hormones combined (group I) and radiotherapy alone (group II) groups, when analysed for biochemical disease-free survival (bNED control) and distant metastases failure (DMF). Statistically significant improvements in bNED control, DMF and cause-specific failure (CSF) were observed for patients receiving LTH compared with STH.

In those patients receiving LTH, the benefit in bNED control (p=0.0002), DMF (p=0.05) and CSF (p=0.02) was limited to centrally reviewed Gleason scores of 7 and scores 8-10 for tumours. For all patients treated on RTOG 85-31, statistically significant improvements for bNED control, DMF, and CSF were observed between groups I and II [18].

There is evidence for a benefit of hormonal therapy when combined with brachytherapy, in a study with similar subset of patients [19]. Low risk patients defined by PSA ≤10 ng/ml, stage ≤T2a, and Gleason score ≤6

did not benefit from neoadjuvant hormonal therapy: 3.8% versus 7.7% positive biopsy rate after treatment, p=0.5. For the high risk patients, that is, the remainder of the patients who did not belong to the low risk group, the results were 3.4% versus 21.1%, p=0.003.

However, the duration of hormonal therapy is still controversial: it can be given as a neoadjuvant treatment and then extended after radiotherapy as an adjuvant treatment. Bolla's study used a total duration of three years [20] and the RTOG study 92-02 used it for two years after external beam radiotherapy.

Salvage hormonal therapy for localised prostate cancer

Timing of hormonal therapy

The NCI study [8] suggested that early total androgen blockade may be advantageous to delayed treatment for patients with metastatic prostate cancer. An analogy may be drawn between patients who have rising PSA after failure of the primary treatment and it is possible that early treatment may improve survival but we need randomised trials to confirm this suggestion.

Delivery of hormonal therapy

Prostate cancer is an androgen-dependent tumour and deprivation of androgen hormone has been the mainstay in the management of patients with distant metastases. Despite an initial response rate of about 80%, predictable and irreversible resistance to androgen deprivation will occur in the vast majority of patients. This progression from initial response is attributed to the fact that surviving tumour cells become androgen-independent [21-23].

Currently there is increasing evidence suggesting that progression to androgen-independence is an adaptive process secondary to androgen withdrawal. In studying mechanisms of progression, Bruchovsky found that, in the androgen-dependent *shionogi* carcinoma model, androgen withdrawal alters the ratio of stem cells in the tumour cell population [24]. Initially there is an elimination of differentiated cells and a decrease in the proportion of tumourigenic stem cell. At the time of progression and recurrence a marked 20-fold increase in the proportion of total stem cells and 500-fold increase in the proportion of androgen-independent stem cells was noted. These data suggest that progression begins early in the disease course secondary to lack of androgen-induced differentiation of the parent stem cells with resultant loss of apoptotic potential [24]. If androgens are replaced before progression begins, the surviving stem cells should give rise to an androgen-dependent tumour susceptible to further hormonal manipulation.

Intermittent androgen deprivation therapy has been studied in animal models. In the androgen-dependent tumour models, investigators found that apoptosis could be re-induced and that this approach prolonged, indeed almost tripled, the mean time to androgen-independent status [25-27].

Clinical data indicate that a satisfactory palliative response can be achieved in patients who have restarted androgen deprivation therapy following a period without any therapy. Prolonged therapy-free intervals of several months could be achieved without apparent adverse effect on survival [25, 26]. This experience in metastatic disease is utilised in the salvage treatment of rising PSA after failure of the primary treatment. It is understood that this salvage treatment is not curative but its use is justified because many of these patients are elderly, and salvage prostatectomy or brachytherapy or cryotherapy has severe treatment morbidity.

In addition, despite the most advanced imaging techniques, it is possible these patients may have micrometastases in the lymph nodes or distant organs. The intermittent androgen deprivation approach is meant to provide treatment to control the tumour, with a potential for prolonged therapy-free intervals resulting in improved quality of life, delay in progression to androgen independence, and reduced cost of therapy. Additionally, the men in this study stand to gain relief from distressing side effects and to regain potency.

The duration of induction therapy is crucial for the success of this approach. The induction duration should be the time required for maximal tumour suppression as represented by PSA nadirs. Current data indicate that 50-80% of metastatic patients will achieve a nadir PSA by 3-8 months following hormonal therapy [28-30].

Since the benefits of intermittent androgen deprivation therapy can only be appropriately evaluated in a randomised fashion, a phase III intergrup study of the National Cancer Institute of Canada (PR.7) and the South-West Oncology Group (JPR-7) is now ongoing.

Total androgen blockade or monotherapy

From the above discussion, one may question the value of a total androgen blockade since the latter may give rise to androgen-independent clones. Also, it is not clear from literature if total androgen blockade is better than monotherapy in terms of overall and progression-free survival.

Conclusions

Hormonal therapy has been considered to be the standard treatment at the time of cancer progression after definitive therapy, and many of the randomised trials have essentially compared adjuvant therapy to delayed therapy. Historical trials using adjuvant hormonal therapy have been limited due to difficulties in clinical staging, as well as toxicities attributed to the formulations used. More recently, hormonal therapy has been found to delay disease progression, increase disease-free survival, and decrease mortality when given immediately after prostatectomy or radiation therapy in selected patients. Neoadjuvant hormonal therapy can improve disease-free

survival and local control when given before radiation therapy; it has only decreased positive surgical margins when given prior to radical prostatectomy but no demonstrated survival benefit from studies to date.

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