Hormonal treatment for progression

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Introduction

A rise of the prostate specific antigen (PSA) following radical prostatectomy (RP) or radiotherapy (RT) with curative intent is the earliest sign of tumour progression. The current definition of tumour progression after RP is a PSA of at least 0.4 ng/mL. Many still consider two consecutive levels of 0.2 ng/mL or greater (EAU guidelines) and further rising; after RT it is defined as a rise of 2 ng/mL or greater above the post-treatment nadir. The prognosis of these patients is very heterogeneous, the relevant prognostic parameters being Gleason score, time to PSA progression and PSA doubling time (PSA DT). Imaging studies are of limited value for the decision on salvage radiotherapy (following RP) as the decision must be taken very early in the course (PSA <0.5 ng/mL) to get acceptable results. Before a local salvage therapy (salvage RP, cryo-surgery, high intensity focused ultrasound [HIFU]) is persued after RT, a biopsy is necessary to confirm local tumour progression and distant metastases should be excluded.

Androgen deprivation is widely applied if curative treatment fails primarily, or if local salvage treatment fails secondarily. However, side effects (osteoporosis, anaemia, cardio-vascular diseases) of long-term hormonal therapy are now increasingly recognised. This has to be taken into account as well as the fact that there is a long interval (median 8 years) from PSA progression to clinical progression after radical prostatectomy, if patients are left untreated [1]. Only about 30% of patients with rising PSA following RP and no further therapy reach the stage of clinical metastases [2]. This seems to be more common after RT (up to 75%). Patients after radical prostatectomy with good prognostic factors (long PSA DT, late PSA relapse, Gleason score <8) have a low risk of dying from prostate cancer within 15 years [3]. These figures must be taken into account when hormonal therapy is decided upon.

When hormonal therapy is considered in this situation, several questions arise: early versus late treatment, continuous versus intermittent treatment, combined androgen blockade versus monotherapy, and luteinising hormone releasing hormone (LHRH) analogues versus anti-androgens

Early versus deferred treatment

Due to the potential adverse effects associated with long-term hormonal therapy, there is an ongoing debate when to initiate this form of treatment i.e. immediately after diagnosis of relapse or when the disease becomes symptomatic [4].

For the PSA relapse situation only retrospective data are available. Moul and colleagues [5] evaluated 1300 patients with a rising PSA following radical prostatectomy. The cut-off for early hormonal therapy was defined at PSA <5 ng/mL. Only patients with adverse prognostic parameters (Gleason score >7, PSA DT <12 months) had a benefit in terms of clinical metastases-free survival whereas no difference was seen for the entire cohort. These results are in-line with others from similar studies. Recently, Studer and colleagues compared the effects of immediate versus deferred androgen deprivation in patients with newly diagnosed, non-metastatic prostate cancer that were not candidates for treatment with potential curative intent in the EORTC study 30891 [6]. Results from this study showed that immediate androgen deprivation resulted in a significant improvement in overall survival compared with deferred treatment (median survival 6.5 years versus 7.4 years), but had a similar effect on prostate cancer mortality and prostate cancer symptom-free survival [6]. However, many of the patients assigned to deferred androgen deprivation did not receive therapy because they had died from other causes before they became symptomatic. Moreover, the overall survival advantage was mainly due to more patients dying from prostate cancer unrelated causes in the deferred treatment arm compared with the immediate arm. Therefore, Studer and colleagues investigated whether serum PSA levels could be used to decide which patients would benefit from early

androgen deprivation therapy (ADT) by analysing patient PSA levels in this study [7]. Results from this analysis showed that patients with a baseline PSA >50 ng/mL and/or a PSA DT of <12 months were at an increased risk of dying from prostate cancer and therefore might have benefited from immediate androgen deprivation. Conversely, patients with a baseline PSA <50 ng/mL and a PSA DT >12 months were likely to die from causes unrelated to prostate cancer and were therefore candidates for deferred treatment [7].

In the Early Prostate Cancer (EPC) programme, the effect of anti-androgen monotherapy with bicalutamide was tested against placebo in several settings [8]. In accordance with the abovementioned results, patients with localised disease did not benefit from early androgen blockade after a median follow up of 7.4 years. In contrast, patients with locally advanced disease profitted in terms of clinical metastases-free survival from early treatment with bicalutamide [9].

In conclusion, few and insufficient data are available to definitely answer the question for early versus delayed hormonal treatment in the rising PSA setting following treatment with curative intent. However, if one transfers the results from studies addressing hormonal treatment in localised prostate cancer, a case for early treatment can only made for patients with high-risk disease (Gleason score >7, PSA DT <12 months). All other patients most probably do not benefit from early hormone therapy.

Intermittent versus continuous ADT

Attempts to enhance outcomes and maximise the success of hormonal therapy studies have involved the use of intermittent regimens, with the hypothesis that off-treatment phases may provide periods of improved quality-of-life (QoL), prolong the time-to-progression to androgen-independent disease and reduce the overall adverse event burden [10–13]. Investigations are continuing to establish the effectiveness of intermittent androgen deprivation (IAD) particularly with respect to optimising the duration of on- and off-treatment periods [11]. To date, several prospective randomised trials have demonstrated that IAD improves QoL during off-treatment and has no negative effects on survival or time to disease progression [14–16]. Tunn and colleagues [14] specifically included patients with a rising PSA following radical prostatectomy. Da Silva and colleagues [15] had a more heterogeneous cohort with 70% M0-patients whereas Miller and colleagues encompassed patients with lymph node and bone metastases.

With the homogeneous results of these three trials, IAD can now be regarded as a valid option for patients with PSA relapse. Patients may benefit in terms of better QoL with no downside effects in terms of progression-free survival. It is not clearly defined, however, when to stop and when to start again with hormonal treatment.

LHRH analogues versus anti-androgens

LHRH analogues are the most commonly used form of hormonal therapy. However, many studies have investigated the use of anti-androgens with the hope of providing a method of hormonal therapy that is as effective as androgen withdrawal, without the associated adverse events of low testosterone levels. Randomised trials have shown less marked reductions in sexual function and reduced loss of bone mineral density (BMD) with anti-androgen monotherapy compared with androgen withdrawal [17]. On the other hand, anti-androgen monotherapy is associated with an increased risk of gynaecomastia and breast tenderness (especially non-steroidal) compared with LHRH treatment [17].

In terms of efficacy it has been demonstrated that anti-androgen monotherapy is inferior with regard to overall survival in patients with metastatic prostate cancer when compared with LHRH analogues [18]. This effect, however, disappears when M0-patients are treated [19], which is in accordance with the theory that anti-androgens are more effective when a low tumour load is present.

Using anti-androgen monotherapy in the rising PSA situation thus seems an appropriate alternative to LHRH analogues including intermittent androgen blockade.

Combined androgen blockade

LHRH analogues are usually co-administered with short-term anti-androgen therapy to reduce LHRH analogue-associated tumour flare. A number of studies have investigated the survival benefits of long-term treatment with LHRH analogues and an anti-androgen (known as combined androgen blockade [CAB]), compared with LHRH analogue monotherapy or orchidectomy alone [20]. The evidence suggests that CAB offers only a modest survival advantage, but results in higher treatment costs [20]. Recent calculations suggest that this small advantage might be of greater magnitude if bicalutamid is used for CAB [21]. However, even when this is taken into consideration, CAB seems not appropriate for the relapse situation

following treatment with curative intent. Here, in view of the potentially long treatment duration, the trend is to reduce the "amount" of androgen deprivation rather than to enhance it. CAB might be considered for second-line hormonal manipulation, if first-line treatment fails [22]. It must be mentioned, however, that all intermittent androgen blockade studies have used combined treatment (LHRH analogues plus anti-androgen). It is not clear if the same effects can be obtained using LHRH analogues alone. In theory, LHRH *antagonists* might be an interesting alternative to the IAB approach, as no flare up occurs with these compounds [23]. However, clinical data with LHRH antagonists in the IAB setting are not available to date.

Conflict of interest statement

None declared.

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