Hormone therapy for prostate cancer

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PSA failure and timing of therapy

A recent study of the natural history of PSA recurrence in 379 patients with PSA recurrence after a radical prostatectomy at Hopkins stratifies patients according to the PSA doubling time and grade, and uses these parameters to predict the likelihood of 5 and 10 year disease specific survival [1].

As the data in Table 1 indicate, the likelihood of prostate cancer mortality varies dramatically depending on PSA kinetics and grade. This has major implications for therapy.

Table 1
10 year prostate cancer specific mortality in men with PSA recurrence after RP [2]

	Recurrence >3 years post RP		Recurrence ⩽3 years post RP	
	Gleason score <8	Gleason score ⩾8	Gleason score <8	Gleason score ⩾8
⩾15 mo	2%	4%	7%	14%
9.0–14.9 mo	5%	10%	15%	31%
3.0–8.9 mo	16%	32%	45%	74%
<3.0 mo	41%	70%	85%	99%

PSA and timing of hormonal therapy

Currently, the commonest indication for initiation of androgen deprivation therapy is a rising PSA after the failure of local therapy. Only one dataset provides evidence for the timing of ADT based on PSA. Moule reported a retrospective series of 1332 patients with PSA progression after radical prostatectomy, of whom 997 received delayed ADT at the time of clinical progression, and 335 were treated with ADT for PSA rise. Overall, there was no difference in the time to androgen independent progression between the two groups. However, the patients with a PSA doubling time <1 year or Gleason 8–10 derived a substantial benefit from early ADT (PSA < 10). In this cohort, the benefit was the same whether the PSA trigger for ADT was 5 or 10.

EORTC protocol 30891 has randomised 985 patients with localised disease to immediate or deferred androgen deprivation therapy. Patients in the deferred therapy group were treated only upon the development of symptomatic bone metastases or local progression with hydronephrosis or retention. This study showed a minor survival benefit (11%) favouring early androgen deprivation. Remarkably, however, the benefit seen was in non-prostate cancer mortality only. There was no difference in the prostate cancer mortality between the two groups. This unexpected finding suggests that the benefit of early androgen deprivation is modest. The study identified subsets of patients who benefited from early deprivation. This included patients under 70 with a PSA < 20, and patients over 70 with a PSA < 50. Patients with a PSA DT < 1 year also benefited. In contrast to the MRC study and the VACURG 2 study, 100% of patients progressing on the deferred arm have received androgen deprivation.

This important study suggests that most patients with a rising PSA should be observed much longer than is currently the practice in North America. The minority of patients with a PSA DT < 1 year or who have high grade disease should have ADT initiated when the PSA is between 10 and 20. For the remainder, the PSA threshold for treatment should be around 20 for men under 70 or 50 for men over 70.

This more conservative approach would spare men a tremendous amount of morbidity related to the systemic and QOL effects of androgen deprivation, and save a considerable amount of money.

Intermittent therapy

Intermittent androgen therapy studies have demonstrated that quality of life is improved by cycling androgen deprivation and avoiding the cumulative side-effects of the regimen. The effect of this strategy on overall and disease specific survival is unknown. This question is being addressed by a phase III prospective randomised trial by the NCIC and the Southwest Oncology Group. The SWOG trial randomises patients who have achieved a normal serum level (<4 ng/ml) of PSA after a 7 month induction period of combined androgen blockade to either

continuous androgen deprivation or to the withdrawal of androgen deprivation with repetitive recycling based on PSA defined trigger points. The NCI Canada trial is testing continuous or intermittent androgen deprivation for patients with a rising PSA after external beam radiotherapy.

Androgen deprivation alone, or combined androgen blockade?

Meta-analyses

Five meta-analyses of MAB versus monotherapy have been published [3–6] and these indicated that MAB provided a survival advantage (risk of death 6–22% lower than for castration alone), which was statistically significant in all but one study. The final meta-analysis was conducted by the US Agency for Health Care Policy and Research and included 21 trials and 6871 patients [5]. No significant difference in overall survival was shown at 2 years, but MAB produced an overall 5-year survival that was significantly greater in the monotherapy group. The magnitude of this benefit was modest, i.e. a 10% reduction in risk of death.

Differences between anti-androgens

Differences have been reported in clinical response to different anti-androgens in the PCTCG meta-analysis. The nonsteroidal anti-androgens flutamide and nilutamide were associated with an 8% decrease in the risk of death (statistically significant for flutamide but not for nilutamide). This compares with a statistically significant 13% increase in the risk death with the steroidal anti-androgen CPA. Differences between nonsteroidal anti-androgens themselves have also been reported. A comparative trial of bicalutamide and flutamide demonstrated greater survival benefits with bicalutamide. Dramatic biochemical responses occasionally occur with bicalutamide in patients failing on flutamide. Toxicity profiles also differ. Diarrhea is common with flutamide, and hepatic toxicity is not rare; pulmonitis occurs with nilutamide. Bicalutamide treatment is not associated with these side effects.

In vitro studies have revealed differences in binding affinity for the human prostate androgen receptor (AR), with bicalutmide having a four times greater binding affinity than shown by 2-hydroxyflutamide and a two times greater affinity than shown by nilutamide. Different nonsteroidal anti-androgens have been shown to differentially block androgen independent activation of the androgen receptor, and to interact differentially with nuclear co-activators and co-suppressors of the AR. These differences could account for the apparent improved response to bicalutamide.

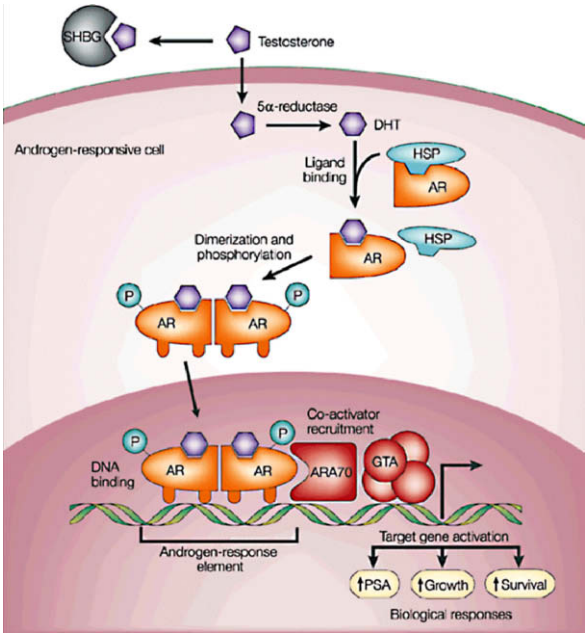

Fig. 1. The androgen pathway. Testosterone circulates in the blood bound to albumin and sex-hormone-binding globulin (SHBG), and exchanges with free testosterone. Free testosterone enters prostate cells and is converted to dihydrotestosterone (DHT) by the enzyme 5α-reductase. Binding of DHT to the androgen receptor (AR) induces dissociation from heat-shock proteins (HSPs) and receptor phosphorylation. The AR dimerises and can bind to androgen-response elements in the promoter regions of target genes. Co-activators (such as ARA70) and corepressors also bind the AR complex, facilitating or preventing, respectively, transcription. Activation or repression of target genes leads to biological responses including growth, survival and the production of prostate-specific antigen (PSA). Reprinted with permission, *Nature Reviews Cancer* 2001, **1**(1), 34–45.

Finally, a re-analysis of the bicalutamide versus flutamide trial, integrating the data with the flutamide versus placebo data, suggests a 20% reduction in prostate cancer mortality using bicalutamide compared to monotherapy with castration [7]. If true, the cost per life year saved of MAB compared to monotherapy compares extremely favourably with interventions for other interventions for cancer.

Identification of androgen-independent disease

Disease progression while on androgen deprivation, whether clinical or bio-chemical, indicates either inadequate androgen deprivation or the development of androgen independence. *Testosterone levels are necessary to insure a castrate level has been achieved.* Testosterone should be <50 ng/ml and optimally <20 ng ml. If the testosterone level is above

these levels, the LH level should be measured to insure adequate LH blockage (should be <1.0). If elevated, attention to dose scheduling or injection protocol needs to be addressed. Occasionally, patients acquire resistance to LHRH analogues. The concept of 'one dose fits all' disadvantages occasional patients. Weight, body surface area and pre-treatment testosterone may render the standard dose inadequate. If LH levels are persistently >1, consider orchiectomy.

Conflict of interest statement

None declared.

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