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Comments and Critique

New Directions With Hormone Therapy in Prostate Cancer: Possible Benefit From Blocking Prolactin and Use of Hormone Treatment Intermittently in Combination with Immunotherapy

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IT IS NOW more than 10 years since the observation that high levels of prolactin were associated with escape from endocrine control in prostate cancer [1]. Despite this, there has been little in the way of large scale effort (apart from a study from Poland [2] using fosfesterol combined with bromocriptine) to really evaluate whether this observation has any clinical benefit.

The sad death of Geoffrey Chisholm whose obituary is on page 861 of this issue coincided with completion by members of his department of a randomised phase 2 trial (see pp. 871–875) which provides the first evidence that compared with total androgen blockade, prolactin blockade by bromocriptine may produce benefit in treating prostate cancer. These authors present both a surrogate endocrine endpoint (i.e. suppression of serum prolactin and androstenedione levels after treatment) and clinical evidence (i.e. shrinkage of the prostate on ultrasound) to support this view. As yet, the data show no evidence of survival advantage. Though this is hardly surprising since the number of patients randomised (30) is totally inadequate to be drawing an unequivocal conclusion, it must be remembered that the benefit of total androgen blockade in the trial of Crawford and associates [3], was far more marked in terms of the immediate response as measured by prostate specific antigen (PSA) response compared with actual survival. As no trial has been performed with the degree of endocrine investigation reported by Rana and associates, and the basic science is so compelling, it would be important that these observations achieve a wider audience in order to promote discussion about setting up larger scale clinical trials to investigate them. However, as the investigation will need to compare single agent versus two versus three drugs, it will be necessary to have a very large trial.

Even more controversial will be the issue as to whether the primary endocrine modality should be orchidectomy alone or gonadotrophin releasing hormone alone. With evidence from three sources demonstrating in small series of 7 [4], 6 [5] and 16 [6] patients, respectively, that periods off hormone treatment in patients achieving PSA complete remission have not produced any detriment to survival, the whole issue of intermittent treatment of patients is another dimension of prostate cancer treatment that needs to be examined. This is needed to exclude the possibility that continuous androgen suppression itself is a selection force for the development of hormone resistance as has been shown so convincingly in the setting of developing antibiotic resistance in bacteria. The limited data in the paper by Oliver and associates [6] suggest that there could be a case for extending the research on short term hormone therapy alone into patients with local disease without radiotherapy. Given the data from Crawford and colleagues' trial suggesting that surrogate indices of immediate response to treatment, i.e. PSA response, were more significantly influenced by total androgen blockade than long term survival, it is possibly that there might be greater benefit from maximum androgen blockade if it is used intermittently. This is why the data presented in the paper by Rana and associates (pp. 871–875) is so important, as combining suppression of gonadal androgen with a prolactin blocking drug (bromocriptine) and adrenal androgen blockade (cortisone acetate) was significantly more effective than combination with flutamide in terms of reduction of prostate size.

At first sight it seems paradoxical that hormone therapy, a treatment that is in theory cytostatic, not cytotoxic, because it only reverts the tumour stem cells to the resting prepubertal state, should have a long-lasting effect in some patients when it is stopped. Because routine hormone profiles were not performed in all the patients given intermittent treatment, it is possibly just a reflection of failure to regenerate testosterone. However, as at least 4 of the patients in one study recovered normal sexual activity [6], this is unlikely to be the total explanation. A more interesting possibility comes from recent reports from the study

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of lymphocyte levels after gonadotrophin releasing hormone (GNRH) analogue treatment showing lymphopenia during the post treatment testosterone surge and lymphocytosis in more than 75% of patients when testosterone reaches castrate levels [7]. This observation is the first confirmation in man of an observation known from studies in rabbits during the 19th century that castration induces regeneration of thymus and thymic-influenced lymphocytes [8]. Further support for this observation comes from a study demonstrating a correlation between thymic size in patients with testis cancer and atrophy of the contralateral testis [9]. If improved immune function was a factor in the prolonged disease-free interval seen in some of the patients after short term hormone therapy, it might be possible to further prolong these remissions by using immunotherapy. There has only been one report of use of immunotherapy in hormone therapy responders. This was a small breast cancer study from Japan and the authors reported that immunotherapy increased progression free survival at 3 years from 13 to 46% [10]. Evidence from the study of bladder cancer treatment with bacillus calmet guerin (BCG) immunotherapy [11] supports the view that immunotherapy is more effective in the earlier and better differentiated tumours as do reports that carcinoma *in situ* of the uterine cervix has a 100% incidence of spontaneous regression after using condoms to block the immuno-suppressive effect of semen [12, 13].

Application of this strategy of short term hormone therapy combined with immunotherapy to the early stage prostate cancer patient and only performing prostatectomy on those who have viable cancer persisting after 3 months therapy could be an interesting new approach to separating the "tigers" from the "pussycats" and reduce the number of prostatectomies being performed in patients with latent tumours which may not be life-threatening [14].

To make large conceptual leaps on the basis of small numbers is always dangerous, however, as the initial report on discovery of B27 in ankylosing spondelitis reporting only 12 cases shows, one does not always need large numbers to demonstrate major effects. The observation about the effects of prolactin are backed by a large experimental database. The differences demonstrable from the combined total androgen and prolactin blockade are so large when compared with orchidectomy plus flutamide that they could open up a totally new dimension to endocrine therapy. This approach may also be relevant to breast cancer. Equally, the concept of intermittent therapy may be relevant to all of the new strategies that are being developed to explore blockade of growth factors and oncogenes in other cancers to avoid expanding endocrine insensitive clones.

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