Summary

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Chairman of such a symposium is the task of summarizing the main points of the meeting, giving a coherent overview. I believe that this meeting was exceptional in looking at some of the controversial issues facing urologists today, and looking at these issues from not only a clinical perspective, but also in terms of providing the rationale and preclinical base upon which many of the strategies are utilized.

Although there is much debate about the possible direct effects of LH-RHa on the prostate cell, the latest research outlining this was clearly presented by Prof. Sica. She demonstrated that leuporelin acetate counteracted the stimulatory action of androgens on the proliferation of hormone-sensitive LNCaP cells. Leuporelin was also confirmed to inhibit the mitogenic action of epidermal growth factor (EGF) in the hormone-insensitive PC-3 cell line. Another important action associated with leuporelin was its ability to reduce prostate-specific antigen (PSA) gene expression in both hormone-sensitive and hormone-insensitive cell lines. These findings demonstrate that leuporelin may act as a negative growth factor, directly regulating cell growth and PSA gene expression. These fascinating results open up a whole new field of future research. Finding answers to these most basic questions regarding the mechanism of action will be extremely important. By identifying how hormone-sensitive and hormone-insensitive cells are regulated, we are paving the way for the continuing development of improved therapeutic strategies aimed at specific cells.

The use of a therapeutic algorithm based upon a nomogram for the management of locally confined tumors (clinical stages T_{1a-c} and T₂) was presented by Prof. Altwein. By using this nomogram, a clinician is able, with a greater degree of certainty, to state which stage a patient is

in and, therefore, determine and tailor the most appropriate strategies for individual patients. Prof. Altwein recommended that patients with T₁ or T₂ tumor, a low grade (Gleason 2–4) and patients greater than 70 years of age should be managed with watchful waiting. All other patients with a locally defined tumor should receive a radical prostatectomy (RP). He further clarified which type of RP should be used in specific patient groups; the type depending on prognostic and clinical factors. For instance, he advocated a nerve-sparing approach only on the opposite side to that of any negative biopsy. A perineal RP was only indicated for small prostates with low tumor burden, and if possible a low Gleason score. If the nomogram predicts extracapsular extension (T₃) then a wide-margin excision is indicated, with adjuvant therapy for cases with positive margins. If it is known prior to surgery that the patient has positive nodes, they should receive androgen deprivation only, unless they specifically wish for RP or are enrolled in a trial.

No clear consensus has yet been reached on the role of neoadjuvant hormonal therapy (NHT), and further data was added to the debate by Prof. Prezioso, who noted that while most studies investigating NHT have shown a decrease in the percentage of positive margins and reduction in tumor volume, no clear advantage for NHT prior to RP has been shown, especially in terms of improved survival or time to progression. Results from Prof. Prezioso's own study revealed that, in patients with clinically localized disease treated with leuporelin acetate and cyproterone acetate (the latter only for the possible flare period), a direct correlation was observed between the histological grade and response to treatment in terms of histological regression. There was a clear trend towards less positive margins in NHT-treated patients. Hormonal de-

privation was able to reduce tumor volume, increase cell death (apoptosis), decrease proliferation activity with absence of mitosis, and reduce vessel density, leading to a reduction in the biological potential of the tumor. Although the urological community still waits for definitive answers to this perplexing problem, it does appear that there is a role for NHT.

The use of radiotherapy in treating locally advanced prostate cancer (PCa) has also been at the forefront of recent urological research, and results from some principal trials in this area were presented by Prof. Bolla. Three randomized, phase III trials assessing androgen suppression using an LH-RHa before and during, or during and after, external irradiation were performed. Results have shown gains in disease-free, local relapse-free and metastasis-free survival, although only the EORTC trials has reported a significant improvement in overall survival ($p = 0.001$). In conclusion, Prof. Bolla noted that the RTOG trials have shown that NHT improved disease-free survival, and in patients with Gleason 8–10 grade tumor there is an increase in disease-free survival. One possible mechanism for this is that hormonal treatment acts outside the pelvis by decreasing the occurrence of micrometastases and may improve apoptotic deaths due to external radiation. This is a promising area in which current research is aimed at optimizing available treatment strategies. The results of these ongoing trials are eagerly awaited to clarify the role of hormonal therapy even further.

Permanent androgen deprivation remains the mainstay of therapy for advanced PCa. However, a great deal

of interest has developed in the experimental intermittent androgen deprivation (IAD) schedules. Prof. Tunn and Prof. Rambeaud reported the use of such IAD treatment for patients with a low tumor burden and those with metastatic disease, respectively. Prof. Tunn reported results from a pilot study which enrolled 44 patients with PSA progression following retropubic radical prostatectomy (RRP) and transurethral resection of the prostate (TURP) with incidental pT1 cancers. Follow-up ranged from 30 to 64 months with no patients becoming androgen-independent over this time. Results confirmed that patients with a low tumor burden were successfully treated with IAD. However, further large trials are needed before the value of IAD can be conclusively proven. Both presenters concluded that IAD offers potential benefits in terms of a possible improvement in disease-free survival (although not confirmed at present). There are other significant benefits in terms of improved well-being for the patient during their off-treatment periods as well as lower health care costs. Certainly these indicate that IAD is an important therapeutic strategy well worth continued assessment.

The treatment of PCa continues to develop with ongoing research helping to clarify how best we clinicians can treat this all too common disorder. I am sure that all participants left this symposium full of renewed enthusiasm for their field of endeavour, including the development of improved treatment regimens. Finally, I would like to express my great thanks to the speakers for providing us with such well presented and thought-provoking reviews, and to Takeda Chemical Industries Ltd. for sponsoring this worthwhile event.