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A New Science Editor for EJC

The Editors of *The European Journal of Cancer* are delighted to announce that Professor Ian Hart is to join the Editorial team as Science Editor. Ian Hart, who is currently a principal Senior Scientist at the Imperial Cancer Research Fund in London, is soon to take up the Richard Dimbleby Chair of Cancer Research at St Thomas's Hospital in London. He is visiting Professor to the Division of Biomedical Sciences at Kings College and has previously worked as a scientist in the cancer biology programme at the NCI Frederick Cancer Research Facility in Maryland, U.S.A. His research activities have been directed towards an understanding of mechanisms underlying invasion and metastases, including signal transduction mechanisms, cell adhesion receptors and tumour-related angiogenesis. Professor Hart's group has recently figured prominently in the news following the announcement of their work on gene therapy for melanoma.

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Comments and Critique

What is the Correct Hormonal Treatment for Prostate Cancer?

ONCOLOGISTS COULD be forgiven for protesting ignorance if asked "What is the optimal hormonal treatment for prostate cancer?" This is because there is no consensus view as to whether combination endocrine therapy with a gonadotrophin releasing hormone (GnRH) agonist and an anti-androgen, or monotherapy with a GnRH agonist alone is the treatment of choice.

The concept of total androgen ablation became controversial 10 years ago when Fernand Labrie publicised its importance. He suggested that in a disease that was androgen sensitive, it was important to deprive the tumour of all sources of androgen. Orchiectomy, whether surgical or medical, leaves the castrated patient with measurable circulating androgens, the sources of which are primarily adrenal and dietary. These low circulating levels of androgens may be of significance in the prostate because of local concentrating mechanisms.

Dr Labrie's work was challenged by Andrew Schally, the Nobel Laureate and joint discoverer of the structure of GnRH. Dr Schally suggested that the concept was irrelevant because it was based on work in a normal animal model. In normal animals there was a synergy of effect between anti-androgen and GnRH analogue in retarding seminal vesicle and prostate growth[1]. His own work on transplanted prostatic tumours showed no synergy of effect [2].

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Despite this challenge and the scepticism in oncological circles that surrounded total androgen ablation, many informed patients pressed for combination endocrine treatment of their cancers. Such was the furore generated by the hypothesis that a National Cancer Institute (NCI)-based investigation was established which was organised by David Crawford. Dr Crawford's study, which was published in the *New England Journal of Medicine* in 1989, showed an advantage of 2 months in terms of response duration and 7 months in overall survival for patients treated with leuprolide and flutamide as compared with those patients treated with leuprolide alone. The study was meticulously conducted and the results were subsequently independently audited and confirmed. Scepticism persists, despite this clear result in a study of over 600 patients[3].

In this issue of *The European Journal of Cancer* (pp. 1088–1093), we publish the findings of the Italian Prostatic Cancer Project Study Group. This trial of 373 patients with locally advanced or metastatic disease compared treatment with goserelin alone or with flutamide. There was no difference in response rates or overall survival between the two patient groups, however, the median follow-up was short at 2 years. In this trial combination therapy led to a more rapid response than monotherapy, but was associated with a 12% incidence of gastrointestinal toxicity.

There are other studies that have examined the value of

combination endocrine therapies. The Danish Prostatic Cancer Group randomised 264 patients with either locally advanced or metastatic disease to either orchiectomy or goserelin, or goserelin with flutamide. A minor advantage was found with combination therapy in initial response rates but not in time to progression or overall survival. The median follow-up of these patients was 30 months [4]. The EORTC urological oncology group randomised 327 patients with metastatic prostatic cancer to orchiectomy or goserelin and flutamide. Time to progression was longer in the combination arm but there was no difference in overall survival. The median follow-up of these patients was 18 months [5]. The International Prostate Cancer Study Group trial of goserelin with or without flutamide found no advantage to combination therapy in an analysis of 571 patients with either localised or metastatic cancer followed for a median of 2 years [6]. The significance of these trials' conclusions is reduced when one considers the short follow-up, mixed patients populations and differences in treatment. A second EORTC study is investigating the benefit of cyproterone acetate given in combination with buserelin. The results of this study have been analysed and no advantage shown to combination therapy according to the trial organiser (J Klijn: personal communication). This latter study could be criticised because cyproterone acetate does have the theoretical disadvantage of inherent androgenicity [7]. This is obviously suboptimal in the context of the concept of anti-androgen treatment limiting the significance of the conclusion of this EORTC study.

The six major trials described above are amongst at least 10 investigations of combination endocrine therapy that are currently underway. These trials are the subject of a meta analysis whose results are eagerly awaited. In any analysis of the advantages of combination therapy, it should be noted that there are disadvantages to treatment with flutamide and these are expense and the 10–15% incidence of gastrointestinal complications. The added expense of treatment can be disregarded in our affluent European societies if the NCI's studies finding of a prolongation of life are confirmed. The gastrointestinal toxicity can usually be moderated by dosage reduction.

In addition to the therapeutic gain in terms of prolongation of remission and duration of life there is another advantage to the concomitant administration of anti-androgens and that is the avoidance of tumour flare. Without anti-androgens, GnRH analogues will cause tumour flare in between 1 and 40% of patients [8]. With co-administration of anti-androgens, this syndrome is virtually unknown [9].

Returning to the question posed by this editorial it would appear that there is no definitive conclusion as yet, as to the benefits of combination therapy in terms of prolonging the patient's life. Whilst awaiting a definitive conclusion, my own view is that we should continue to recommend combination therapy because of the significance of the NCI study's findings and because of the advantage of avoiding tumour flare.

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Should Further Studies of Chemotherapy be Carried out in Pancreatic Cancer?

DEFEATISM AND nihilism are not prominent in the therapeutic vocabulary of surgical oncologists. Nevertheless, certain malignancies defy even the most aggressive intellects and resist all attempts to improve survival. Pancreatic cancer is a classical example. If resectable and localised the cancer should be removed, for after all, this is the only hope of cure. But what if it is irresectable, as in the majority of patients? Palliation by stents or surgical bypass is valuable but will not significantly improve survival. Intuitively, but with a degree of scepticism, one may seek a solution in cytotoxic chemotherapy. This can be used either as an adjuvant in patients who have undergone resection, or for the treatment of advanced and inoperable disease. Such therapy, however, can lead to intolerable cytotoxi-

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