Basic Science/Medicine

MONDAY 30 OCTOBER 1995

Teaching lectures

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CANCER DRUGS CLINICAL PHARMACOLOGY: RELEVANCE IN ONCOLOGY

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Anticancer drugs have a narrow therapeutic window and drug level monitoring in plasma can aid to individualize chemotherapeutic strategies and prevent patients being under- or overdosed. Defining the most optimal plasma levels of a drug and/or its metabolites is one of the major challenges in current clinical pharmacological research. It requires the performance of population based kinetic studies to obtain insight into the pharmacokinetic-pharmacodynamic relationships. It must be emphasized, however, that clinical pharmacological investigations are surrounded by many pitfalls which may concern the sampling, storage of the samples, analytical procedures and interpretation of the data. Although research on the clinical pharmacology of anticancer drugs is increasingly appreciated by medical oncologists now its relevance for daily clinical practice is becoming more and more evident it is still not a daily routine but will become so in the near future.

2

LOCO-REGIONAL RECURRENCES OF BREAST CANCER AFTER RADICAL AND SEGMENTAL MASTECTOMY

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The detection of a loco-regional recurrence after primary treatment for breast cancer is a common event in clinical practice. Data from the literature are compared to those obtained from the analysis of a series of 4344 patients submitted to radical mastectomy (2948 pts., median follow-up: 15 years) or segmental mastectomy plus radiotherapy (1879 pts., median follow-up: 6 years). A total of 666 loco-regional relapses were observed: chest wall: 274, lymph-nodes: 231, breast: 79, multiple sites: 82. The incidence of synchronous metastases (28.9% in the total group) was respectively 25.5%, 36.4%, 5%, and 42.7%. Nodal involvement, pT diameter and the administration of adjuvant chemo or hormonotherapy significantly affected the appearance of chest-wall and nodal recurrences. The appearance of breast relapses mainly depended on age at surgery and by the administration of adjuvant hormonotherapy. Survival from relapse was significantly influenced by pT diameter and nodal involvement at surgery, by the length of disease-free interval and by the extention of the relapse.

3

RANDOMIZED CLINICAL TRIALS IN ONCOLOGY: TOO MANY OR TOO FEW?

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Despite the long-standing, often emotional, debate of the pros and cons of the randomized controlled clinical trial, this remains the ultimate tool for testing the clinical value of any new treatment regimen. In cancer therapy, a large number of questions can only be answered by this method. In this sense, more randomized trials are needed. On the other hand, an overview of published randomized trials shows that many of these are subject to methodological problems and that they quite frequently include a number of patients which will only allow resolution of drastic improvements in treatment outcome. In this sense, too many randomized trials are being conducted. The lack of resolution in many trials is the rationale behind 'mega-trials' which are designed to include a large number of patients often from multiple centers, with broad patient inclusion criteria, and often with patient survival as the only endpoint. However, the biological heterogeneity of human cancer means that this approach may fail to detect very significant improvements in more homogeneous subgroups of patients. In this teaching lecture, I will review some of the principles in the design and conduct of randomized clinical trials. Among the topics discussed are planned interim analyses, multiple endpoints, and quality assurance procedures. Finally, I will try to make the case for trials with a specific biological rationale.

4

REGIONAL TREATMENT WITH TNF-ALPHA AND CHEMOTHERAPHY

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Isolated limb perfusion (ILP) may be used in cases when a malignant tumour has spread extensively in a single limb. It implies the surgical isolation of a limb, its connection to a heart-lung machine and the perfusion of high dose cytotoxic agent.

ILP with melphalan produces a 50% complete remission rate in melanoma and a 6% in sarcoma of the limbs. In order to improve these results, recombinant Tumour Necrosis Factor-alpha (rTNFα) was added to melphalan and rIFN-γ in ILP for in-transit melanoma metastases, irresectable soft-tissue sarcomas and carcinomas of the limbs. A 90% complete response rate was obtained for melanoma (Liénard D *et al.*, *Melanoma Res.* 1994, **4**, S1: 26-26,), a 36.4% complete response rate for sarcoma (Eggermont A. *et al.*, 1995, submitted) and a 57% complete response rate for squamous cell carcinoma invading the bone. Angiographic, immunohistological and immunological studies suggest that the efficacy of this protocol is due to dual targeting: rTNFα activates and selectively lyses the tumour endothelial cells, whilst melphalan acts mainly as a cytotoxic agent against the tumour cells. ILP with rTNFα appears to be a useful model for studying the biochemotheraphy of cancer in humans.

5

CLINICAL EXPERIENCE WITH CONFORMAL RADIOTHERAPY

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Over the past decade, we have gained considerable experience with conformal radiotherapy. A series of dose escalation studies in brain, lung, liver, and prostate have been carried out. In high grade gliomas, we have completed the 70 Gy (n = 20) and 80 Gy (n = 35) series of patients. Median survival is 16 months, and we have escalated to 86 Gy. In lung, our dose prescriptions are based on the amount of normal lung treated. In our smallest tumors, we have reached a dose of 92 Gy. In primary liver tumors, we have escalated small volumes of liver (<1/3rd of the organ) to 72.6 Gy and have achieved a 70% actuarial rate of local control. In