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Teaching lectures

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PROBLEMS, OF DRUG DEVELOPMENT AND REGISTRATION IN EUROPE

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The current European Application Procedures—Centralized, Decentralized, and National—are well adapted to Drug Registration in the EU. The specific problems of anticancer agents—phase I trials in patients, lack of well accepted surrogate end-points, value of phase III single agents trials, role of Quality of Life measures, general use in the context of combination and multimodality therapy—are poorly understood by some Agencies. A better interaction between Oncologists and Agencies is needed as well as clarification of these points.

Drug development raises more questions. (1) Only a minority of Early Clinical Trials are performed in Europe. (2) Few indications are targetted—Breast, Lung, Colorectal, Ovarian Carcinomas. (3) Less frequent cancers are not studied as soon as registration is obtained in one major indication therefore accounting for wide off-label prescriptions. A process allowing for alteration of the SPC on the basis of well conducted Institutional trials should be considered together with appropriate cost adjustments. (4) Pharmacovigilance of antineoplastic agents is almost non existent. (5) Further trials addressing dose-intensity as well as atypical combinations (i.e double alkylation) are examples of non approved procedures which ultimately might legally involve Oncologists.

As Registration can be acquired early, and further use of the agent can be looked without modification of the SPC, one can expect than Social Security and/or Insurances will limit the use of recently approved agents to the legal indications. It is thus the responsibility of the Oncology Community to (1) Participate in prospective trials; (2) organize consensus conference to define the State of the Art in the use of anticancer agents.

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NEW DEVELOPMENTS OF NUCLEAR MEDICINE IN DIAGNOSIS AND TREATMENT: THE PRETARGETING APPROACH

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Specific targeting of radioactive agents to tumor cells has been a major goal of the *in vivo* use of monoclonal antibodies (MoAb) for diagnostic and therapeutic purposes. However, only a relatively small amount of the injected dose of MoAbs is bound by the tumor, while MoAb conjugated to radioisotope keep circulating in the blood stream and in normal tissue. These considerations have led to strategies of tumor pretargeting, where MoAb and radiolabel are administered separately. One of these strategies is based on the avidin-biotin system. With the so-called three-step method, injection of non-radioactive biotinylated MoAbs (first step) is followed after 1 day by "cold" avidin (second step). If radioactively labelled biotin is now administered (third step), it binds selectively to avidin and therefore to the tumour, including colon and lung cancers, gliomas, ocular and cutaneous melanomas and apudomas. The method has shown to be safe, reliable and of clinical utility since an overall sensitivity of 88% with 94% specificity and 84% accuracy was demonstrated. These encouraging results have prompted us to initiate a therapy trial using biotin-LC-DOTA labeled with Y-90.

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GENETIC ALTERATIONS IN BREAST CANCER

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The etiology of breast cancer involves a complex interplay of various factors, including genetic alterations. Many studies have been devoted to the identification and characterization of mutations that occur frequently during breast tumorigenesis. The major types of genetic abnormalities frequently observed in breast tumor DNAs are amplification of proto-oncogenes (*MYC, ERBB2*) and chromosome band 11q13, mutation of *TP53*, and loss of heterozygosity (chromosomes and chromosome arms 1, 3p, 6q, 7q, 8p, 11, 13q, 16q, 17, 18q and 22q). Genetic deletions and mutations could inactivate tumor-suppressor genes. Recently, linkage analysis of large families with a predisposition to breast cancer have been performed in order to map breast cancer susceptibility genes (*TP53, BRCA1, BRCA2,* ...). The findings have thrown light on the molecular mechanisms of breast cancer, and have enabled various genetic markers to be used in clinical oncology.

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THE ROLE OF BRACHYTHERAPY IN THE TREATMENT OF CERVICAL CARCINOMA

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Brachytherapy (BT) plays an essential role in the local control of cervix carcinoma. Numerous applicators have been designed for intracavitary BT. Among them, custom-made vaginal moulds fit the anatomy of the vagina and the topography of the tumor. Dose prescription has been frequently reported at a single point, the Manchester point A. More recently, ICRU Report 38 has defined a reference volume of the 60 Gy isodose, specific envelope reference points associated with normal tissues (bladder, rectum, pelvic side walls). The ICRU recommendations also include the description of the technique. The aim of this Report 38 is to uniform the dosimetry report and to find correlations between dosimetric characteristics and complications.

Interstitial BT techniques were developed for bulky parametrial or vaginal involvement or vaginal or limited central recurrences. A higher incidence of severe complications was observed with this approach.

Traditional dose-rate in gynecological BT is low-dose rate BT. More recently, high-dose rate BT was used in cervical carcinoma. Two randomized trials showed results in favour of high-dose rate BT, but other authors have described a higher incidence of complications when the dose rate increases.

More clinical studies are required to better define the exact role of high dose rate in the therapeutic approach of cervical carcinoma.

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CANCER IN THE ELDERLY

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Although cancer is not an inevitable consequence of aging, malignant diseases, especially solid tumors, occur disproportionately in the subset of the population aged 65 years and older. Thus, because the older population are rapidly expanding in most industrial nations, there is a high potential in these countries for many more persons to have cancer. Although two thirds of all cancer deaths occur in the 65-and-older age segment of the population, there have been so far only a few descriptive,