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CANCER GENETICS: TUMOR BIOLOGY AND GENOME TECHNOLOGY CONVERGE

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Cancer is a genetic disease of the somatic cell. The long known multistep nature of neoplasia and clonal evolution of tumors, reflect sequential genomic alterations ranging from chromosomal aberrations to point mutations. These events affect the structure and/or function of specific genes whose products control essential processes such as cellular proliferation and structure, programmed cell death, and DNA replication and maintenance. While most of these alterations occur in somatic cells, some may be transmitted through the germ line and render the carriers predisposed to cancer. Most of the genes involved in cancer predisposition, initiation and progression can be divided into three main groups: 1. Tumor suppressor genes, whose products serve to control cellular proliferation, and whose inactivation removes "brakes" that prevent the cell from embarking on the neoplastic pathway. Notable examples are genes involved in predisposition to retinoblastoma, Wilm's tumor, colon cancer, and the neurofibromatosis type 1 and p53 genes. 2. Protooncogenes, or dominant oncogenes, which express their oncogenic potential when activated by point mutations or other mechanisms that enhance their expression. These genes are believed to act mainly in the advanced stages of carcinogenesis, enhancing the neoplastic phenotype in its more aggressive stage. 3. Genes for the chromosomal instability syndromes, which are responsible for a group of autosomal recessive disorders manifested by developmental disturbances, genomic instability, susceptibility to DNA damage and cancer predisposition. Xeroderma pigmentosum, ataxia-telangiectasia (A-T) and Fanconi's anemia are examples of these disorders. A-T carriers, estimated at 1% of the general population, are also cancer-prone.

Identification of the functions of these genes should lead to new means of early and presymptomatic diagnosis of cancer, and to novel treatment and prevention strategies. Considerable progress was made in the identification of these genes using the new technologies developed for the study of the human genome. Three basic approaches to the identification and functional analysis of human genes are being used: positional cloning, functional complementation of the cellular phenotype and creation of animal models. Detailed genetic maps, and techniques created in the human genome project are expected to rapidly expedite this research. These approaches will be demonstrated using representatives from each of the three groups of genes involved in cancer.

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ADJUVANT TREATMENT IN COLO-RECTAL CANCER

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RHABDOMYOSARCOMAS IN CHILDREN : CURRENT THERAPEUTIC APPROACH

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These two last decades have been marked, not only by **an improvement of the therapeutic results** obtained in USA by the Intergroup Rhabdomyosarcoma Studies (IRS) and in Europe by the International Society of Pediatric Oncology (SIOP) and other European teams, but mainly by a **progressive international agreement** on the pathological classification, the modalities of staging and grouping by sites, the choice of a unique staging system, the definition of common and clear end-points allowing comparable statistical evaluation of the therapeutic trials.

According to the international pathological classification, RMS are divided into 3 prognostic subtypes =1) favorable : botryoid and leiomyomatoid types (15%) ; 2) unfavorable : alveolar (solid variant included), 20% ; 3) intermediate : embryonal (65%).Immunocytochemistry is the preferred method of diagnosis ; moreover, after cytogenetics has lead to describe the t(2;13) (q35;q14) in alveolar RMS, molecular biology technics (in situ hybridization) should allow to detect a specific rearrangement on 13q, useful for diagnosis, prognosis, evaluation of minimal residual disease and response to treatement.

The following interelated variables are prognostically significant : 1) **Stage** : TNM clinical and post-surgical staging system now preferred to single post-surgical system (previous IRS groups) ; 2) **primary sites** ; 3) **pathological types** ; 4) **response to treatment.** The prognostic value of DNA content (favorable hyperdiploidy vs diploidy-aneudiploidy) and its possible correlation with chemosensitivity is currently assessed. New studies will clarify controversial data on the prognostic value of increased expression of MDR1 gene, the potential role of p53 and of genes of myoid cell differentiation (myoD1).

Current therapeutic approaches combine surgery, radiotherapy (XRT) and chemotherapy (CT) according to sites, stages and histological types. **Surgery**.Primary excision is decided according to its completeness (clear margins, assessed if necessary by a reexcision),the preservation of the function and cosmetics considerations. Biopsies of suspected lymph nodes is preferred to radical lymphadenectomy. A delayed and conservative excision may be feasible after primary CT (f.ex:in bladder-prostate sites). The decision of a 2nd look surgery has been underlined to assess the response to previous treatments (s) and to take the best choice of further therapy. Surgery has also to be debated in relapsing and metastatic patients. **Radiotherapy**. Dose-response data for XRT, taking into account the efficacy of CT and the long-term sequelae, are urgently needed . 45 to 55 Gy are usually delivered by conventional XRT on macro and/or microresidual tumour according to the trials. After primary complete excision (favorable histology), XRT is useless (IRS I).The highest importance of early XRT has been demonstrated in high-risk parameningeal sites by IRS II. In the other sites, after biopsy or partial excision, the aim of IRS trials is still to obtain a prompt local response combining early XRT and CT ; otherwise, the philosophy of SIOP trials is to avoid XRT and its sequelae, expecting the efficacy of CT to eradicate microresidual disease, but exposing to a higher rate of local relapses. Brachytherapy allows to sterilized small endocaviteal or superficial RMS, without important sequelae. Hyperfractionation is under study to increase local response and decrease long-term effects. **Chemotherapy**. The major active drugs have been indentified in Phase II trials in relapsing patients and the increased survival rate using adjuvant CT based on VAC-pulse regimen has been demonstrated 15 years ago. Other single drug combinations have been furtherly tested, including ifosfamide, CDDP, VP16, DXR, melphalan, not only in re sistant pts but as front-line theapy in high risk patients. As survival rate has been improved by increasing repetitive doses of CT, the use of hematopoietic growth factors to increase and/or to compress doses and courses of CT is under study, nevertheless the role of high-dose CT followed by ABMT has not been demonstrated in metastastic or relapsing patients. **Combined-modality therapy**. General **principles** are based on the analysis of survival rates, prognostic factors and sequelae of IRS and SIOP trials. Primary site, extent of the disease, histological subtype, feasibility of initial complete excision , age of the patient and quality of the response to primary chemotherapy in unresectable patients constitute the criteria of the best therapeutic choice.

Results ***In IRS trials, I, II, III** (1972-91), 5 yr survival rate in non metastatic patients, increased from 63 to 75%. Majority of patients have been irradiated and received VAC pulse regimen ±DXR ±CDDP ±VP16. Important messages are related to :- the role of early XRT in high-risk parameningeal patients ; - the efficacy of intensified CT allowing to delay the local treatment in bladder-prostate RMS and to retain bladder in 65% of them. ***In SIOP MMT 84** (84-89), 5 yr survival rate in non metastatic pts is 69 % vs 52% in MMT 75 (75-84). As regard to the local control, obtained in 90% of cases, the objective was to decrease the risk of sequelae (conservative surgery , no XRT or only delivered on a reduced volume), using courses of IVA (ifo-VCR-ACD) as first line and CDDP-DXR as 2nd line. That goal has been attained since 55% of pts in continuous complete remission did not receive an agressive local treatment (only 37 % have been irradiated). However the high rate of relapses (42%) lead to modify the guidelines in **MMT 89** : intensified primary CT to increase complete response after incomplete surgery, earlier local treatment in poor responders. 2 yr survival rate in the MMT 89 is 87%.

Results remain very poor in stage IV patients whatever the trials, with a 5 yr survival rate of 20 %, without any benefit of high dose CT and ABMT.

In conclusion, a more comprehensive approach of this very heteregeneous group of tumors has improved the survival rate and the quality of life of the pts. For the future, a possible molecular classification of RMS could open new therapeutic approaches based on other antimitotic drugs and differentiation agents.