12

DIAGNOSIS AND TREATMENT OF NEURO-ENDOCRINE TUMORS

Schlumberger M. Institut Gustave Roussy F. 948058 Villejuif Cedex

The term Neuro-Endocrine (NE) has gradually replaced APUD (Amine Precursor Uptake and Decarboxylation). While NE neoplasms presenting with a clinical syndrome of hormonal hypersecretion are uncommon, tumors that are entirely or predominantly composed of cells with NE differentiation are common and have been described in virtually every organ system of the body. Some of these tumors are familial and/or multiple. They exhibit a wide variety of morphologic patterns and diagnostic techniques include : examination by light microscopy: histochemistry : NE cells are argyrophilic (Grimelius Stain) : immunohistochemistry : neuron-specific enolase is a sensitive but non-specific marker : two markers are highly specific, chromogranin A and synaptophysin, but this may be difficult to demonstrate : neuropeptides and their precursors such as calcitonin, ACTH, somatostatin and VIP. These substances, measured in the serum may be used as tumor markers; electron microscopy : neuroendocrine granules. Histologic classification takes into account both the origin of the tumor and the degree of differentiation. Well-differentiated tumors are in general slow growing and have a relatively good prognosis : in the absence of metastasis, the differential diagnosis between benign and malignant may pose a problem. Anaplastic NE carcinomas progress rapidly and are less frequently associated with clinically recognizable excess hormone production. The main treatment of differentiated NE tumors is surgery. Responses to Interferon and Somatostatin analogs mainly consisted in a reduction in tumor marker levels and an improvement in clinical symptoms. Scintigraphy with a somatostatin analog may predict response to therapy. Tumor response to 131 I MIBG therapy in tumors with a high uptake (i.e. pheochromocytoma) is about 20 % with functional improvement in another 30 %. Chemotherapy has been used in some large series of NE tumors : the combination of Etoposide and cisplatin produced a high response rate in anaplastic NE tumors but was almost ineffective in well differentiated tumors. Currently, standard chemotherapy for well-differentiated tumors combined at least two of the following drugs : 5 FU, Doxorubicin, Streptozocin, DTIC, Cyclophosphamide. Response rate changes with the origin of the tumor.

13

CHEMOTHERAPY IN THE ELDERLY

S. Monfardini, Division of Medical Oncology, Centro di Riferimento Oncologico, Aviano, Italy.

Cancer is a disease which affects primarily older persons. At present over half of all cancers are diagnosed in patients over 65 years, but as our aging population increases, the incidence of cancer will rise. Adequate dosage of chemotherapy is fundamental to achieve response in patients with advanced cancer, but comorbidity is often a problem in older patients who need also a multidimensional assessment before and after treatment (evaluation of physical health, activities of daily living, mental status, cognitive functioning, quality of life).

Results from prospective studies on the intensity of the dose of chemotherapy administered to elderly patients are not available. Administration of more intensive multiple drug regimens has restricted older patients' inclusion in protocols without any corresponding improvement in alternative treatment options, especially in haematological malignancies. However the use of hematopoietic growth factors (G-CSF) will probably allow the increase of dose intensity of chemotherapy in older patients. Evaluation of kidney and liver function together with nutritional status (albumin level and relative increases in body fat) are at present primary determinants for dose adaptation of many chemotherapeutic agents. Pharmacokinetic studies may however also help to define peculiar patterns of drug disposition in elderly patients and thus provide guidelines for adequate drug dosing. Minimal sampling techniques are available allowing this kind of studies also in elderly patients. A very small minority of elderly patients has been so far included in chemotherapy research protocols prepared for adults but there is a body of evidence that selected elderly patients with good performance status and adequate organ function can be entered in clinical trials without an increase of excessive toxicity and early discontinuation of treatment. Psychological adaptation to disease and treatment may be even better in elderly patients. While are lacking results of trials in which for the elderly has been followed the same therapeutic approach used in adults, those of specifically designed studies for a really representative population of elderly patients have been providing still preliminary and quite scarce data. Therefore it is concluded that:

1. Since being treated in clinical trials means a better standard care, elderly patients should not be discriminated in their access to clinical trials, even if they are over 70 years.
2. Controlled clinical trials specifically devised for elderly patients are needed.
3. A multiparametric geriatric assessment is essential to guide the administration of cancer chemotherapy and evaluation of its results.
4. For all clinical trials in older persons a close cooperation is needed among medical oncologists, geriatricians and family physicians.

14

MOLECULAR BASIS OF THE CELLULAR RESPONSE TO IONIZING RADIATION Simon Powell, Dept. of Radiation Oncology, Massachusetts General Hospital, Boston, Mass., USA.

Cells and tissues have developed a variety of ways of responding to a hostile environment, be it from drugs (toxins) or radiation. Three categories of damage limitation are: (i) DNA repair (ii) changes in cellular metabolism (iii) changes in cell interaction (cell contact or tissue-based resistance; whole organism based resistance). Most literature about radiation response concerns DNA damage and repair. However, it is becoming increasingly recognized that DNA damage not only leads to its repair, but also triggers a spectrum of damage response genes with effects upon cellular and intercellular metabolism

DNA repair will be discussed under the following headings: repair-deficient mutants and repair genes; radiation resistance induced by gene transfer; DNA repair mechanisms in response to ionizing radiation; DNA repair, the cell cycle and the role of cell cycle arrest in response to damage. A number of human ionizing radiation repair genes are at various stages of cloning and isolation. The function of these genes are not known. Other radiation-sensitive genetic conditions, for example the *scid* mutation in mice, have suggested links between DNA recombination and repair of ionizing radiation damage. Yeast radiation-sensitive mutants have linked various recombination functions and radiation resistance. The DNA transfer of vectors containing oncogenes or mutant tumor suppressor genes has been reported to alter radiation resistance. The controversy about *ras* will be discussed together with p53 mutants. The use of specifically constructed DNA repair probes to delineate repair mechanisms, and the DNA changes in radiation-induced mutations will be outlined. The relationship between cell-cycle arrest and radiation resistance can sometimes correlate closely, but exceptions to this association are reported.

Changes in cellular metabolism as a result of ionizing radiation can impart radiation resistance, which is usually transient rather than permanent. Radiation-induced changes in protein expression include: GADD (growth arrest and division delay proteins) and p53; XIP (X-ray induced proteins) which lead to transient resistance; "early-response" genes, such as c-fos, c-jun, Egr-1; growth factors, such as FGF, PDGF, TNF. The outcome of these cellular responses to radiation determine whether the cell undergoes proliferation arrest and DNA repair or conflicting proliferation signals and apoptosis.

Possible mechanisms for intercellular resistance could include: cell-cell contact via gap junctions and metabolic resistance to radiation from an effective cell pool; paracrine response mechanisms such as growth factors leading to the protection of a group of cells from the response of a fraction of that group, the upregulation of MDR channels may allow the release angiogenic factors such as FGF leading to tissue and/or tumor radiation resistance.