



P.S. Oncologia L. 449/97

**NATIONAL RESEARCH COUNCIL**

**MINISTRY OF EDUCATION,**

**UNIVERSITY AND RESEARCH**

## **ABSTRACT OF:**

### **1.0 BASIC ASPECTS**

#### **Pharmacological and biological rational of interaction between chemical and physical therapies.**

Experimental studies have helped clinicians to change physiological characteristics against the tumor, such as hypoxia, in a therapeutic advantage.

The knowledge of molecular and biochemical process, linked up with hypoxic tumoral condition, has permitted to define and use with success a type of drugs in the clinical practice which can develop their cytotoxic function thanks to a selective activation in hypoxic conditions. Therefore they can be utilized in locoregional therapies of hypoxic tumors, or in case of hypoxic condition obtained artificially from appropriate techniques.

In oncology the word hyperthermia refers to the treatment of neoplastic pathologies with heat given in different methods. Hyperthermia is generally applied to the patient in combination with other therapeutic modalities. Clinical studies have demonstrated a rise in the local control and in the survival if applied locoregional hyperthermia treatment combined with radiotherapy in patients having superficial tumors, locally advanced or recurrent, or with pelvic tumors.

Pre-clinical studies have permitted to understand either the molecular effects of hyperthermia or the mechanistic basis relative to the strengthening of chemotherapy effects. All that contributes to the rational design of new therapeutic strategies with combination.

## **Hypoxia**

### **Molecular effects**

Owing to the scarce and anomalous vascular development most of the solid tumors present medium levels of pO<sub>2</sub> which are lower than those ones of the tissue of origin; moreover the hypoxic zones are characterized from low levels of pH and glucose.

The hypoxic microenvironment in the solid tumors affects both tumoral cells and also the non-neoplastic stromal cells, such as macrophages and fibroblasts. Furthermore it gives a greater aggressiveness to tumor and an increased metastatic potential.

Hypoxic environment is able to select expressions of cells which have mutated the gene p53 by losing in that way their apoptotic potential and by acquiring instead an advantage of growth.

Hypoxia supplies the tumoral cells with a microenvironment which makes radio- and chemo-resistance easier. For over 50 years it has been known that hypoxic tumoral cells are decidedly more ionizing radiation-resistant than oxygenated cells. Several studies on patient with soft tissue sarcomas and uterine cervix cancer have proved that the presence of hypoxic area in the tumoral mass affects, in an adverse way, the loco-regional control of the illness and the free interval after primary radiotherapy.

## **Bioreducing drugs**

The strategies, which have been adopted till now in order to overcome the hypoxic cell resistance to treatments, are based on:

- i) improvement of oxygenation in tumors by using hyperbaric oxygen or oxygen-mimetic drugs;
- ii) use of bioreducing drugs with specific selectivity for hypoxic cells.

Drugs of this category include 2-nitroimidazole, misonidazole, which has not been used anymore in hospital because of its high neurotoxicity, and the 5-nitroimidazole, nimorazole which has demonstrated its capacity to improve the therapeutic effects of ionizing radiations in some oral cavity tumors against a modest toxicity.

In order to overcome either chronic or transient hypoxia in tumors, it has been used the combination of carbogen (a mixture of 95% O<sub>2</sub> and 5% CO<sub>2</sub>) with vitamin B derivative, nicotinamide, in combination with standard or accelerated radiotherapy.

## **Hyperthermia**

### **Molecular effects**

From 1960s several studies have proved that the exposure to high temperatures (from 41°C to 47°C) can determine the tumoral cell death by creating therefore a dependence on the temperature.

The survival curve of the cell to hyperthermia treatment, as a function of exposure time, shows a typical “shoulder shape” which reflects a biophasic cell death process. Said process is characterized from a linear stop-growing in the beginning of the exposure to heat (indicative of a sub-lethal and reversible effect), followed from an exponential phase of cell death.

Several studies have demonstrated that the hyperthermia treatment determines modifications to cellular membrane such as changes in fluidity and stability, changes in electric potential and in transmembrane transport, accompanied from a modulation of transmembrane-pump activity (MDR, etc.).

Besides that the treatment of hyperthermia interferes directly with nucleic acids metabolism by inducing inhibition in DNA and RNA synthesis, changes in DNA structures and inhibition in the activity of DNA enzyme of reparation (Dahm-Daphi et al., 1997). Changes in protein synthesis have been observed in cells which were subjected to a treatment of hyperthermia, accompanied to a protein denaturation, aggregation of proteins to the nuclear matrix and induction of HSP synthesis.

## **Hyperthermia and chemotherapy**

Many experimental studies have clearly demonstrated that hyperthermia can strengthen cytotoxic activity of antitumoral drugs with different action process. The importance of this thermic chemosensitization is valued as a relation between cytotoxic effect of a particular drug under a certain concentration in hyperthermic conditions and in normal temperature conditions. The type of interaction between heat and drugs has been classified in:

- i) “additive/over-additive” effect, when there is a linear increase of the drug cytotoxic activity with the rise in temperature (from 40,5°C to 43°C). Said effect is observed with bifunctional alkylating agent (melphalan, cyclophosphamide and ifophosphamide) and compounds of platinum (cisplatinum, oxaliplatinum);
- ii) “threshold” effect, when there is a strengthening of the cytotoxic activity of the drug below a certain temperature (>42°-43°C). At present all data at disposal can show that the best thermic chemosensitization effects, for most of the studied antitumorals, are obtained when heat and drug are given simultaneously or at a short intercurrent interval, even if there are some exceptions connected essentially to the activation process of the drug.

## **Future prospects**

In spite of the experimental studies have helped to clarify the molecular processes of hyperthermia and the mechanistic basis of thermic strengthening of some conventional drugs, new biological studies are now necessary to assess the activity of recent antitumoral compounds in hyperthermic conditions and to provide with rational basis for the design of new thermo-chemotherapy protocols.

Future applications of hyperthermia are at present in a period of study in sectors of genetic therapy, with particular reference to generation of expression vectors, in which the therapeutic gene is kept under the control of promoter of HSP and under the control of pharmacology, through the use of liposomes which are able to release the drug in such a way depending on the temperature.