CHAPTER 10

Thermo-Chemo-Radiotherapy Association:
Biological Rationale, Preliminary Observations
on Its Use on Malignant Brain Tumors

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Abstract
This chapter focuses on the biological rationale and the advantages for combining hyper­
thermia radiotherapy and chemotherapy. Other clinical aspects such as sequence of
administration, effects on drug uptake and methods used to improve the efficacy of
HT are also discussed. The actual applications and effects of HT on brain are presented. Fur­
thermore, the preliminary clinical results obtained, by our group, on malignant brain tumors
using this triple combination of cure are illustrated. The survival curves of brain tumors in total
and of glioblastomas, treated with HT, were compared to the single standard application of
conformational radiotherapy. The life quality and survival results are favorable to HT, however
the number of patients treated is limited. In every case we suggest its use for better clinical
control of the disease.

Radiotherapy and Hyperthermia Interaction

Hyperthermia Killing Curves (Arrhenius Relationship)

Heat cell killing occurs exponentially as a function of time and dose and its shape is not
dissimilar from those obtained for X-rays (Fig. 1A). The data in vitro are consistent with results
in vivo and they show that a relatively small changes in temperature can have a large effect on
cell killing.¹³

Another way to describe the kinetics of tumor cell killing is to use the Arrhenius relation­
ship. This analysis relates time and temperature and it is the basis for the calculation of thermal
activation energy.² Arrhenius plot (Fig. 1B) shows that the reciprocal of D₀ values plotted
versus reciprocal of the absolute temperature 1/T results in a straight line and it permits to
calculate the activation energy required to obtain thermal damage. The dramatic change of the
slope of the curve occurring over 43°C, called the break point, means that the activation energy
is different below and above this point, reflecting a different mechanism of cell killing.⁴ Above
43°C the activation energy for heat toxicity is similar to that for protein denaturation suggest­
ing that the target is a protein (chromosomal proteins, nuclear matrix repair enzymes,

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membrane components); below the break point thermotolerance can develop gradually during the heating suggesting a cell adaptability (see Thermotolerance paragraph). The Arrhenius plot can be modified by different factors such as pH, step-down heating, some chemotherapeutic drugs, ATP status, cell cycle phase, Bioflavonoids and CoX2 inhibitors.

**Hypoxia, pH**

Blood perfusion in large solid tumors is generally poorer than that in normal tissue. The vascular beds in tumors are chaotic and poorly organized resulting in temporal and spatial unbalanced blood supply. Therefore, many regions within tumors result hypoxic / acidic and resistant to radiation and chemotherapy. The chronic or transient deficiency in tumor perfusion can generate state of chronic or acute hypoxia. Chronic hypoxia develops when cancer growth outstrips its blood supply, reaching a critical mass > 1-2 mm³ (10⁹ cells) and a distance from host nutritive vessel > of 100-200 μm (Fig. 2). Regions of transient hypoxia can develop within tumor mass following a temporary interruption of blood flow. Transient perfusional hypoxia is caused by various mechanisms. The most plausible ones seem to be:

a. Irregular expansion of tumour mass, whose three dimensional growth is subjected to a continuous remodelling, in a confined space, causes a temporary compression or occlusion of some tumour capillaries (Fig. 3).

b. Transient stop of tumor blood flow or supply by platelets plug. In our opinion, this intravascular thrombosis deserves to be taken into much higher account than usually done. In fact, the majority of cancer patients has coagulation abnormalities associated to hypoxia. Recently, it has been demonstrated that hypoxia not only induces VEGF but also stimulates endothelial cells to over express tissue factor (TF) and plasminogen activator inhibitor (PAI-I). These factors induce endothelium to become prothrombotic and cause fibrin formation and platelet activation. Furthermore, VEGF binds to fibrinogen and fibrin by stimulating...