EUROPEAN JOURNAL OF CANCER 44 (2008) 2546–2554

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Current Perspective

Hyperthermia adds to chemotherapy ☆

Rolf D. Issels[*]

University of Munich – Campus Grosshadern, Medical Clinic III, 81377 Munich, Germany
HelmholtzZentrum München, Institute for Molecular Immunology, 81377 Munich, Germany

ARTICLE INFO

Article history:
Received 29 May 2008
Received in revised form 17 July 2008
Accepted 24 July 2008
Available online 11 September 2008

Keywords:
Hyperthermia
Chemotherapy
HSP
Immunology
Liposomes
HIPEC
ILP

ABSTRACT

The hallmarks of hyperthermia and its pleotropic effects are in favour of its combined use with chemotherapy. Preclinical research reveals that for heat killing and synergistic effects the thermal dose is most critical. Thermal enhancement of drug cytotoxicity is accompanied by cellular death and necrosis without increasing its oncogenic potential. The induction of genetically defined stress responses can deliver danger signals to activate the host's immune system. The positive results of randomised trials have definitely established hyperthermia in combination with chemotherapy as a novel clinical modality for the treatment of cancer. Hyperthermia targets the action of chemotherapy within the heated tumour region without affecting systemic toxicity. In specific clinical settings regional hyperthermia (RHT) or hyperthermic perfusion has proved its value and deserve a greater focus and investigation in other malignancies. In Europe, more specialised centres should be created and maintained as network of excellence for hyperthermia in the field of oncology.

1. Hyperthermia or heat shock exposure: Arrhenius relationships from the molecule and cell to the clinic

Hyperthermia can be defined as controlled temperature elevation by targeting the heating field to the malignant tumour as well as the surrounding tissue, organ, part of body or even to the whole body. Following the results of profound research starting in the early 1970s for exponentially growing cells when exposed to heat shock above a threshold temperature – in general – a strict temperature–time relationship was noted. This is specific for the individual cell line, and different in the various phases of the cell cycle using clonogenic cell death as an end-point.[1] The thermal energy dose for induction of cell death was found to be closely related to the amount of energy required for cellular protein denaturation. This led to the conclusion that the direct cytotoxic effect of hyperthermia itself is mainly based on denaturation of nucleolic, cytoplasmatic or membrane proteins. Based upon complete sets of survival data testing different cell lines, Arrhenius blot relationships were performed to allow the numerical description and calculation of the thermal dose achieved during a certain exposure time at a given temperature.[2]

Calculation of the thermal dose applied in hyperthermia has been successfully integrated into the concept of a 'thermal isoeffect dose' (TID).[3] By the TID concept, heating time periods at different temperatures are converted into equiva-

☆ *Source of support*: Helmholtz Gemeinschaft Deutscher Forschungszentren – VH-VI-140 Clinical Hyperthermia and Related Technology SFB455 – Virale Funktionen und Immunmodulation Deutsche Krebshilfe e.V.

* Tel.: +49 89 70954768; fax: +49 89 70954776.
E-mail address: rolf.issels@med.uni-muenchen.de.

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.07.038

lent heating minutes at 43 °C. For consecutively applied heat treatments, the TID for each single treatment can be added to give the cumulative equivalent minutes at 43 °C (CEM_{43}). When treated with heat shock, mammalian cells develop a transient resistance to subsequent heat exposure. This phenomenon has been called 'thermotolerance' and is at least partially due to the induction of heat shock proteins (HSPs) and other post-transitional adaptation processes (e.g. cell cycle arrest in the G2-phase). The TID calculation is complex and is influenced by a number of environmental factors as well as by the transient development of thermotolerance. However, it at least allows to predict the outcome *in vitro* for a given heat dose.

There is no intrinsic difference between heat sensitivity of normal and tumour cells *in vitro*. There is, however, a tumour-selective effect of hyperthermia at temperatures between 40 °C and 43 °C *in vivo*. The architecture of the vasculature in solid tumours is chaotic, resulting in regions with hypoxia and low pH levels, which is not found in normal tissues under undisturbed conditions. These factors turn cells more sensitive to hyperthermia especially in low perfused areas. Therefore, in addition to direct cytotoxicity, hyperthermia leads *in vivo* to an almost selective destruction of tumour cells in hypoxic and, consequently, acidic environment within parts of solid tumours.[4,5] Despite complexity and limitations of thermal dose dosimetry, the notion is that thermal dose, quantified by the TID concept as CEM 43 °C, is related to outcome in randomised studies, both in canine[6] and in human[7] tumours.

2. Enhancement of drug cytotoxicity by hyperthermia: its reality at clinically relevant temperatures

Heat modifies the cytotoxicity of many chemotherapeutic agents (see Table 1).[8–13] The extent of 'thermal chemosensitisation' both *in vitro* and *in vivo* can be quantified by the quotient of the clonogenic cell growth or tumour cell growth or tumours treated either with the drug alone or with the same drug at elevated temperature. The thermal enhancement ratios (TER) for certain antineoplastic agents at two different temperatures (41.5 °C *versus* 43.5 °C, respectively) are given in Table 2. The TER mainly represents the pharmacodynamic features of the drug-heat-interaction. More recent *in vivo* studies have demonstrated that the thermal enhancement of cytotoxicity of many chemotherapeutic agents is maximised at temperatures between 40.5 °C and 43.0 °C.[14] The mechanisms of interaction *in vitro* are tested on the basis of an isobologram analysis.[15,16] Synergism is observed as a continuous change with increasing temperatures of the rate at which cells are killed by the drug. It is generally accepted that most alkylating agents (e.g. cyclophosphamide and ifosfamide) and platinum compounds as well as the nitrosoureas

Table 2 – Thermal enhancement ratio (TER) of selected chemotherapeutic agents

Drug	Treatment time (min)	TER	
		41.5 °C	43.5 °C
Cisplatin	30	1.48	1.59
Cyclophosphamide	30	2.28	2.74
Ifosfamide	30	1.52	–
Ifosfamide	90	3.60	–
Melphalan	30	3.60	–
BCNU	30	2.27	2.71
Bleomycin	30	1.24	1.65
Mityomycin C	30	1.05	–
5-Fluorouracil	30	1.0	1.0
Doxorubicin	30	1.0	1.0

Data taken from Urano et al.[103]

Table 1 – Overview of the interactions between some chemotherapeutic agents and heat

Class of agent		Interaction	Remarks
Platinum drug	Cisplatin	More than additive	Gradual increase with increasing temperature; highest when simultaneous
	Carboplatin		
Alkylating agents	Cyclophosphamide	More than additive	Gradual increase with increasing temperature; highest when simultaneous
	Ifosfamide		
	Melphalan		
	Mitomycin		
Nitrosources	Carmustine (BCNU)	More than additive	Highest when simultaneous
	Lomustine (CCNU)		
Antibiotics	Bleomycin	More than additive	Only >42 °C; largest when simultaneous
	Doxorubicin	Complex	Less than additive when heat precedes drug
	Actinomycin D		
Pyrimidine antagonists	5-Fluorouracil (5-FU)	Independent	No interaction
	Cytarabine (Ara C)		
Vinca alkaloids	Vincristin	Independent	
	Vinblastin		
Taxanes	Paclitaxel	Complex	Cell type dependent; temperature 41.5–43.0 °C
Nucleosidanalog	Gemcitabine	Additive	Only if applied 24 h before or after heat

Derived and adapted from Kampinga.[102]