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# Hepatic Thermochemotherapy

Mark A. Burton, Debra K. Kelleher, James P. Codde and Bruce N. Gray

HEPATIC THERMOCHEMOTHERAPY of the liver has been assessed with radiofrequency or microwave hyperthermia and several different anti-cancer drugs, especially 5-fluorouracil, methotrexate and dacarbazine. However, doxorubicin *in vivo* and *in vitro* has significantly elevated activity at about 43°C, although toxicity may be increased [1]. We have examined the response of experimental liver tumours to low-dose doxorubicin plus regional hepatic hyperthermia.

20 New Zealand white rabbits (both sexes, 3.0–4.5 kg) had VX2 carcinoma implanted into the right and left medial lobes of the liver. 16, 17 and 18 days later, 10 rabbits received a 15 min intravenous infusion of 0.08 mg/ml doxorubicin to a total of 1.2 mg/kg. On day 18 a further 5 animals had their exteriorised livers exposed to microwaves ("Radarmed 12 T202", Bosch) at 2450 (S.D. 50) MHz. This provided a thermal dose of 30 min at 43°C measured at two sites in each of the tumours by fluoroptic thermometry ("Model 3000", Luxtron). 5 of the doxorubicin-infused animals were additionally treated with hyperthermia and the remaining untreated rabbits acted as controls.

All animals tolerated both the hyperthermia and doxorubicin treatments without event and maintained body weights within 10%. Liver function was similar in the control and treated groups. Mean white cell count for the rabbits treated with doxorubicin was 12.9 (S.D. 1.4) $\times$ $10^9$/l; normal range 3.0–12.5 $\times$ $10^9$/l. There were no outward indications of liver damage related to doxorubicin or hyperthermia in any of the groups.

All animals were killed at 28 days postimplantation. Gross observations of control tumours showed a large multilobular diffuse mass of irregular shape, actively invading the surrounding parenchyma; the tumour had developed from a spherical mass of about 10 mm in diameter at 18 days to 30–50 mm at death. Tumours in the doxorubicin-infused animals were semi-spherical and 15–25 mm. There were small areas of incursion of tumour into the surrounding normal tissue. Tumour appearance was similar in the hyperthermia-treated animals, except the central portion of the tumours was avascular and necrotic (about half the mass). Central tumour necrosis was also seen in the rabbits treated with hyperthermia and doxorubicin. Additionally, the dimensions of the tumour had only increased to 9–18 mm. The tumour mass was essentially the same spherical shape as was noted before treatment and confined to the site of implantation.

Mean (S.D.) tumour mass was 8.75 (3.93) g for the controls, 4.84 (1.35) g after doxorubicin, 4.54 (0.39) g after hyperthermia and 2.18 (0.41) g after the combination treatment. Mean tumour mass for all treatment groups was significantly ($P < 0.0001$, $t$ test) decreased compared with controls. There was no significant difference between the hyperthermia and doxorubicin alone groups but the combination treatment mean was significantly ($P < 0.001$, $t$ test) reduced compared with both single treatments.

*In vitro* studies have shown biphasic activity for doxorubicin during heating—above 43°C activity is significantly increased [2]. However, *in vivo* increased efficacy occurs at 41–42°C [3]. Another study reported increased activity at elevated temperature and supra-additive lethality at 40–45°C [4]. The mechanisms may be related to heat-induced impairment of cellular efflux of doxorubicin or to inhibition of repair mechanisms [5].

We found an additive therapeutic response of doxorubicin combined with hyperthermia at 43°C compared with either treatment alone. The dose of doxorubicin was low, as shown by the lack of suppression of white cell count, and was chosen to avoid increased toxicity when combined with hyperthermia. No systemic or local toxicity was encountered in any of the treatment groups. Similar additive responses to low-dose doxorubicin (combined with other cytotoxic drugs) and hyperthermia have been described for oat cell carcinoma of the lung [6]. Significant toxicity and mortality can occur with other combination treatments [1].

Correspondence to M.A. Burton.
The authors are at the Department of Surgery, University of Western Australia, Royal Perth Hospital, Perth 6001 Australia.

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# Unendurable Symptoms as Prognostic Indicators of Impending Death in Terminal Cancer Patients

Vittorio Ventafridda, Carla Ripamonti, Marcello Tamburini, R. Barrie Cassileth and Franco De Conno

PROGNOSTIC indicators of impending death can provide helpful guidance for physicians and nurses caring for terminal cancer patients, enabling them to implement timely therapeutic strat-

egies to keep patients comfortable [1] and to respond to the patients' and families' queries and needs [2]. Unfortunately, prognostic information obtained by clinical observation tends to overestimate length of survival [3–5], even when predictions are made close to the patient's death [4], and regardless of who makes the prediction [3, 4]—general practitioners, hospice physicians, general hospital physicians, nurses or social workers.

Research indicates that the frequency and severity of pain and dyspnoea increase as cancer patients approach death [6–8]. In the last days of life, dyspnoea is the major uncontrollable, severe symptom [9]. For dyspnoea and other problems, patients can be best cared for and made most comfortable when clinicians are alerted to their prognostic importance.

We studied prospectively 120 consecutive patients (73 men and 47 women) with terminal cancer. They were followed up daily until death, by a palliative home care team. In 63 patients (52.5%) 80 episodes of symptoms that patients called unendurable and that physicians termed difficult to control occurred. These symptoms included: dyspnoea (33 patients), pain (31), delirium (11) and vomiting (5). In Table 1 we indicate the frequency of these symptoms in relation to time of death. They occurred in 96.8% of patients within a week of death, and in over half within the last 24 hours (mean 49.2 h, S.D. 65.7, range 2–400).

These observations confirm the frequent increase of physical suffering in the last days of life. Our long-term clinical impression is that the appearance of unendurable symptoms and the aggravation of previously controllable symptoms can serve as important prognostic indicators of impending death, permitting timely intervention that will preclude or reduce problems perceived as unendurable by patients.

*Table 1. Onset of symptoms difficult to control in 63 terminal cancer patients in relation to time of death*

| Time (h) | No. of patients | Cumulative % |
|---|---|---|
| within 24 | 37 | 58.7 |
| 25–48 | 9 | 73.0 |
| 49–168 | 15 | 96.8 |
| 240 | 1 | 98.4 |
| 400 | 1 | 100.0 |

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Correspondence to V. Ventafridda.
V. Ventafridda, C. Ripamonti, M. Tamburini and F. De Conno are at the Pain Therapy and Palliative Care Division, National Cancer Institute, Milan, Italy; and R.B. Cassileth is at the Cancer Center, Hospital of the University of Pennsylvania, Philadelphia, PA, U.S.A.

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# Aromatisation of Dehydroepiandrosterone by Hormone Dependent Human Mammary Cancer MCF-7 Subcellular Fractions

## Abderrahim Najid

SOME BREAST tumours can aromatise androgens into oestrogens [1]. We report aromatisation of dehydroepiandrosterone (DHEA) by MCF-7 human mammary cancer cells.

MCF-7 cells from fourteen T150 flasks ($4 \times 10^8$) were detached, homogenised and centrifuged. Each subcellular fraction was incubated with 10 μmol/l DHEA, 10 nmol/l 1, 2, 6, 7 ($^3$H)-DHEA, 10 μmol/l NADPH and 10 μmol/l NADH. The incubation was continued for 1 h at 40°C in 40 ml 50 mmol/l Tris–HCl (pH 7.0) 1 mmol/l EDTA, 0.1 mmol/l dithiothreitol, 10 mmol/l $MgCl_2$. The reaction was stopped and the steroids extracted twice with 140 ml ethylacetate/cyclohexane (50:50), purified and analysed [2]. After extraction, organic phase products were subjected to ion-exchange chromatography. Neutral and phenolic fractions were analysed by high-performance liquid chromatography. Steroids were characterised by gas chromatography/mass spectroscopy.

Recovery of the incubated radioactivity in the organic phase was over 94%. Solvent lysis of aqueous phase and analysis of the steroids indicated DHEA sulphate and tritiated water. Tritiums (C1 and C2) were eliminated from 1, 2, 6, 7 ($^3$H)-DHEA as tritiated water by the aromatase system. The main conversion of DHEA into oestradiol was obtained with 1000 *g* supernatant and 100 000 *g* pellet. Aromatisation of DHEA by 15 000 *g* pellet may be due to contamination of the mitochondrial fraction by microsomes. Except for the 15 000 *g* supernatant, percentages (Table 1) of DHEA aromatisation were in agreement with microsome localisation of the aromatase system.

Androstenedione was the main metabolite of DHEA. This indicates that an indirect pathway is probably involved in the conversion of DHEA into both oestrone and oestradiol. DHEA was also metabolised into 5-androstenediol and testosterone.

Correspondence to A. Najid, C.J.F. INSERM 88-03 (Prof. Rigaud), Faculté de Médecine, Université de Limoges, F-87025 Limoges, France. A. Najid was previously at the Laboratoire de Biochimie, Faculté de Pharmacie, Université de Limoges, Limoges, France.