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Hepatic Thermochemotherapy

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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].

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

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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-