DDT Vol. 6, No. 15 August 2001

Cancer drug delivery is hot stuff

Martina Habeck, Freelance writer

There is increasing evidence that hyperthermia at 40–43°C enhances the uptake of therapeutic agents into cancer cells and provides an opportunity for improved targeted drug delivery. This message received much attention at the *2001 American Society of Clinical Oncologists (ASCO) Meeting* in San Francisco, where one of the leading manufacturers of hyperthermia equipment, BSD Medical Corporation (BSDM, Salt Lake City, UT, USA), organized a minisymposium to inform delegates about recent advances in the field. Hyrum Mead, President of BSDM, says, 'A significant proportion of the medical oncologists in the USA either attended, or requested information from our symposium. As a result of the meeting and other activities afoot supported by leading oncologists, Medicare reimbursement could be forthcoming for the combination of chemotherapy and hyperthermia, just as it already exists for hyperthermia combined with radiation.'

One reason for the increased interest in combining chemotherapy or biological therapy with hyperthermia is that the available equipment for tumour heating has been substantially improved. Hyperthermia applicators emit radio frequency, microwave or ultrasonic energy into the patient to provide tumour heating (invasive and noninvasive techniques). Invasive hyperthermia devices that produce heat directly within the tumour by placing a microwave antennae within the tumour ('interstitial hyperthermia'). By contrast, non-invasive 'superficial hyperthermia' devices deliver energy through the intact skin and are used to treat tumours that are close to the surface of the body. BSDM's contribution to the field is 'deep regional hyperthermia', which, says Harley Griffith, Director of Sales at BSDM, enables the energy to be focussed on tumours that are deep within the body without using invasive techniques. The use of multiple applicators positioned around the patient make it possible to steer the heating pattern (Fig. 1).

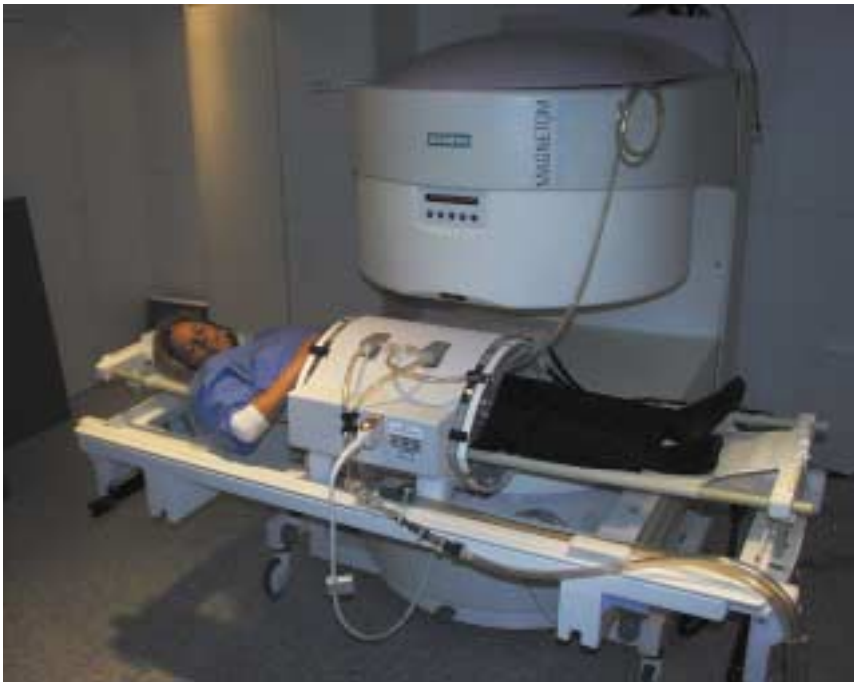

Figure 1. A woman is being treated with the BSD-2000 3D/MR hyperthermia system. The circular device around her body contains 24 dipole radiators. The microwave energy that is being sent out can be focussed on any tumour within the boundaries of the applicator. The device is best used for tumours of the abdomen, pelvis and extremities.

Effects of heat

Several mechanisms contribute to the effects seen with hyperthermia. Because tumours are poorly vascularized, it can be hard for therapeutic agents to reach their target. Heat increases the perfusion of a tumour and, as a result, drugs are transported more effectively into the target tissue.

Moreover, heat makes blood vessels more permeable to drugs. Mark Dewhirst at Duke University Medical Center (Durham, NC, USA) explains: 'This occurs preferentially in tumours, where blood vessels tend to be structurally incomplete. Whereas normal blood vessels are surrounded by a basement membrane and other perivascular cells and are not significantly affected by heat, the blood vessels in tumours have large pores and are more leaky initially. Heat induces disassembly of the cytoskeleton, which results in even larger pores' (Fig. 2).

Griffith points out that heat might also have other effects that are not directly related to improved drug delivery. 'Heat can also potentiate the effect of some drugs, by stimulating chemical reactions. In addition, there are effects on the

1359-6446/01/$ – see front matter ©2001 Elsevier Science Ltd. All rights reserved. PII: S1359-6446(01)01901-8

immune system, triggered by heat-shock proteins.'

Heat-induced delivery of liposomes

Among the results reported at the BSDM symposium were those from scientists at Dewhirst's laboratory. They are investigating the efficacy of hyperthermia as an adjunct to cancer therapy with liposome-encapsulated drugs[1]. Dewhirst says: 'We have found that hyperthermia increases the rate of liposome leakage into tumours by a factor of 2–5, depending on the particular tumour type we are looking at. There is no enhancement of liposome leakage in normal tissues with heating, at least in the range of 40–42°C.'

The group currently have several Phase I studies running, partly in collaboration with BSDM, that are examining the effect of hyperthermia on treatment with:

- Doxil™ (liposomes loaded with doxorubicin; manufactured by Sequua Pharmaceuticals, Menlo Park, CA, USA) in patients with recurrent ovarian cancer and in patients with locally advanced breast cancer; and
- Evacet™ (liposomes also loaded with doxorubicin, but made up of different lipids; manufactured by The Liposome Company, Princeton, NJ, USA) in patients with locally advanced breast cancer.

According to Dewhirst, the therapies are well tolerated. Although Phase I trials are not designed to measure efficacy, there are clear effects. The Evacet trial should progress to Phase II trials within 2001.

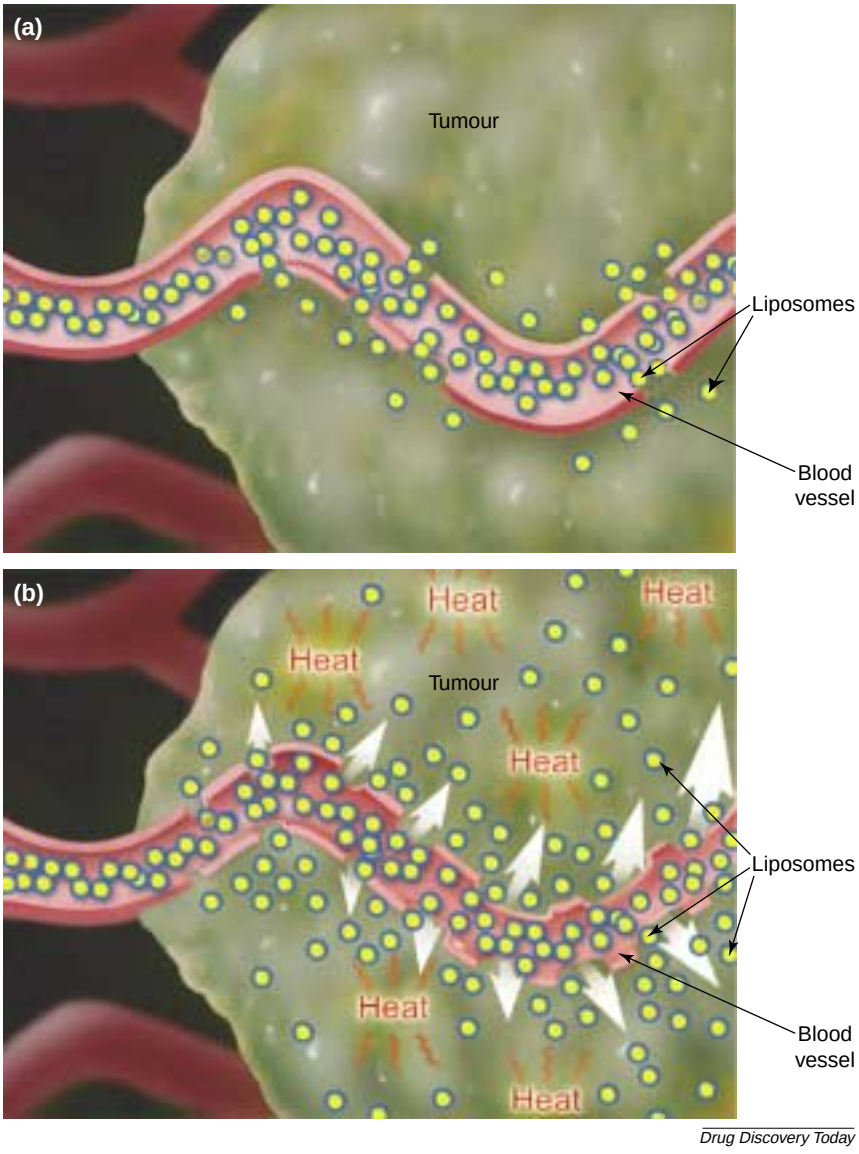

Figure 2. (a) The leakiness of tumour vessels allows some liposomes to escape into the tumour at normal temperatures. **(b)** Heat increases vessel leakage of liposomes by a factor of 2–5 beyond what is seen at normal temperatures.

Hyperthermia-regulated gene therapy

The scientists at Duke University are also experimenting with a new approach to target the expression of interleukin-12 (IL-12) in cancer cells. This work is partly being sponsored by the National Institute of Health (Bethesda, MD, USA) and the Celsion Corporation (Columbia, MD, USA), another hyperthermia equipment manufacturer. In mice, IL-12 has shown strong anti-cancer effects and appears to act synergistically with radiation. However, it is associated with systemic toxicity. The team at Duke University, therefore, constructed an adenoviral vector coding for IL-12 under the control of the heat-inducible promoter of a human heat-shock protein. When they injected the vector as an adjunct to radiation therapy in mice carrying a melanoma line and performed hyperthermia, they found an improved response to radiation therapy without systemic side effects[2].

Dewhirst says, 'We are very excited about new hyperthermia devices that can deliver power to specified regions of the body, thereby taking advantage of the liposomal and gene therapy technologies that are under development. We are still in the investigational stages, but it looks as if taking advantage

of the thermal effects below 43°C will make hyperthermia easier to implement.'

References

1 Kong, G. *et al.* (2000) Hyperthermia enables tumor-specific nanoparticle delivery: effect of particle size. *Cancer Res.* 60, 4440–4445

2 Lohr, F. *et al.* (2000) Enhancement of radiotherapy by hyperthermia-regulated gene therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 48, 1513–1518

Drug-free tolerance of transplanted tissue

Jo Whelan, Freelance writer

Successful organ transplantation could be possible without the need for long-term use of immunosuppressant drugs. Work recently published demonstrates that diabetic monkeys given transplanted pancreatic tissue have remained in good health for more than one year after just two weeks of immune-modifying therapy[1].

Patients receiving transplants currently need to take expensive immunosuppressant drugs for the rest of their lives to prevent rejection of the donated organ. These inhibit the division of T and/or B lymphocytes. Although effective in the short-to-medium term, this regimen has not significantly improved long-term organ survival. For example, only 50% of all kidney transplants are still functional after ten years, the remainder failing as a result of acute or chronic rejection. In addition, the long-term use of immunosuppressants causes a range of side-effects including kidney toxicity, hypertension, diabetes, increased risk of cancer, susceptibility to infection, excessive hair growth and gastrointestinal disturbances.

Inducing tolerance

Because of these side effects, there is considerable interest in modulating the immune system so that transplanted tissue is tolerated without general immunosuppression. Some of this work has focused on isolated pancreas islet allotransplantation (IPIT), a promising treatment for type 1 (insulin-dependent) diabetes. The islet cells of the pancreas are the site of insulin production, and in type 1 diabetes these cells are destroyed by autoimmune attack. Transplanting clusters of islet cells into the liver can reinstate normal blood-glucose regulation[1], but immunosuppressive therapy is required. Even with this therapy, immune-induced deterioration of the cells often gradually reduces insulin output.

The ultimate goal of IPIT would be to treat type 1 diabetes in children before they develop the long-term complications associated with hyperglycaemia, but this is not currently an option because immunosuppressants produce side effects similar to, or worse than, diabetic complications.

A team from the University of Alabama at Birmingham (UAB; Birmingham, AL, USA) has induced 'operational tolerance' of IPIT in monkeys with streptozotocin (STZ)-induced diabetes, a well known animal model of the disease[2]. Operational tolerance is defined as the durable survival of islet allografts without maintenance by immunosuppressive therapy and without rejection or loss of functional islet mass or insulin secretory reserve.

Eleven rhesus monkeys underwent IPIT with donor cells that were deliberately mismatched for major histocompatibility complex (MHC) antigens. Immediately before and after transplantation, nine of the monkeys were given a 100 mg kg^{-1} bolus infusion of $F(Ab_2)$-IT (an anti-CD3 immunotoxin made by conjugating the $F(Ab_2)$ fraction of FN18 anti-rhesus CD3 monoclonal antibody with CRM9 mutant diphtheria toxin), which depletes the lymphoid system of all T cells[3]. Seven of the monkeys were then continuously infused with 2.5 mg kg^{-1} day^{-1} of 15-deoxyspergualin (DSG) for 14 days, which inhibits the nuclear translocation of nuclear factor kappa-B (NF-κB), and thereby blocks both proinflammatory cytokine production and the maturation of dendritic cells[4]. DSG is known to have a strong synergistic effect with anti-CD3 immunotoxin, which is thought to result from a coincidental reduction in lymph-node T-cell mass and mature dendritic cells. This situation, although transient, is thought to favour the development of a stable tolerance to transplanted material.

In all monkeys, non-fasting blood-glucose levels returned to normal within 72 h of IPIT. Rejection of the transplant occurred at 15 and 16 days in control monkeys given only DSG, and at 23 and 70 days in monkeys given only $F(Ab_2)$-IT. However, six of the seven monkeys treated with both agents still had stable blood-glucose levels after more than a year, without any further use of immunosuppressants or insulin.

1359-6446/01/$ – see front matter ©2001 Elsevier Science Ltd. All rights reserved. PII: S1359-6446(01)01899-2